

EXHIBIT 1

BAYER HEALTHCARE LLC, BAYER
HEALTHCARE PHARMACEUTICALS INC.,
and ONYX PHARMACEUTICALS, INC.,

Plaintiffs,

V.

MYLAN PHARMACEUTICALS INC.,

Defendant.

[illegible]

C.A. No. 15-114-LPS
CONSOLIDATED

OPENING EXPERT REPORT OF MARK D. HOLLINGSWORTH, PH.D

TABLE OF CONTENTS

	<u>Page</u>
I. INTRODUCTION	1
II. QUALIFICATIONS AND EXPERIENCE	1
III. SUMMARY OF OPINIONS	4
IV. BACKGROUND	5
A. Crystals, Crystal Forms, and Polymorphs.....	5
B. Thermogravimetric Analysis (“TGA”)	10
C. Thermal Properties.....	11
D. Melting Point	12
E. Differential Scanning Calorimetry (“DSC”).....	12
F. Powder X-ray Diffraction (“PXRD”)	13
G. Calculated PXRD Pattern Based on Single Crystal Data	20
H. Hot-stage Microscopy	22
I. Infrared Spectroscopy	23
1. Mid-IR region	23
2. Far-IR (FIR) region.....	24
3. Near-IR (NIR):.....	25
J. Raman spectroscopy	25
K. Inherent Properties of Physical Forms.....	26
L. Salt Formation.....	26
M. Mixtures and eutectic points	28
V. U.S. PATENT NO. 8,877,933	32
A. The ’933 patent	32
B. Asserted Claims	33

C.	Priority Date	35
D.	Disclosure of the Patent	35
E.	Prosecution History of the '933 Patent	38
F.	The Indian Opposition	40
G.	The European Opposition	41
VI.	SORAFENIB TOSYLATE AND ITS CRYSTAL FORMS	41
A.	The Energy Temperature System of Sorafenib Tosylate Polymorphs and Pseudopolymorphs	42
B.	Sorafenib Base	46
VII.	BAYER'S INVESTIGATION INTO THE POLYMORPHISM OF SORAFENIB TOSYLATE	46
A.	Bayer's Procedures	46
B.	[REDACTED]	48
C.	[REDACTED]	50
D.	[REDACTED]	51
E.	[REDACTED]	52
VIII.	THE METHOD OF EXAMPLE 1 PRODUCES POLYMORPH I, NOT II	61
A.	[REDACTED]	61
	[REDACTED]	63
	[REDACTED]	64
	[REDACTED]	65
	[REDACTED]	65
	[REDACTED]	70

5.	[REDACTED]	70
	[REDACTED]	70
B.	Polymorph II Was Made by a Different Method	74
1.	[REDACTED]	74
	[REDACTED]	74
	[REDACTED]	75
	[REDACTED]	75
C.	All Reported Attempts to Reproduce Example I have Produced Polymorph I.	76
1.	The Indian Opposition	76
2.	The European Opposition	77
3.	[REDACTED]	77
4.	[REDACTED]	78
IX.	LEGAL BACKGROUND	78
A.	Level of Ordinary Skill in the Art.....	78
B.	Priority Date and Prior Art.....	80
C.	Anticipation.....	80
D.	Obviousness	81
E.	Obviousness-Type Double Patenting.....	82
F.	Inventorship	82
G.	Legal Presumption	83
X.	PRIOR ART AND DOUBLE PATENTING REFERENCES	83
A.	WO 03/068228 (“WO 228” or “Dumas”))	83
B.	U.S. Patent No. 7,351,834 (“the ’834 patent”)	84

C.	U.S. Patent No. 8,618,141 (“the ’141 patent”)	85
D.	Art Related to the Preparation of Salts	86
E.	Sorafenib	87
XI.	CLAIM CONSTRUCTION	88
XII.	INVALIDITY OVER THE PRIOR ART AND INVALIDITY DUE TO DOUBLE PATENTING	88
A.	Polymorph I is Inherently Anticipated (or Obvious Over) Conventional, Prior Art Methods of Making Tosylate Salts	88
1.	The Metastable Polymorphs and the Solvates Are Not Made by Conventional, Prior Art Methods	90
(i)	Polymorph III was not the product of conventional methods	90
B.	Polymorph I is Inherently Anticipated (or Obvious) by Standard Analytical Techniques	92
C.	Polymorph I is Obvious Because it is the Most Stable Form at Room Temperature	94
1.	Scope and Content of the Prior Art for Obviousness and Scope of the Earlier-expiring claims	95
2.	Motivation to Identify the Most Stable Form and Expectation of Success in Obtaining the Most Stable Polymorph	95
(i)	A POSA Would Have Had an Expectation that Sorafenib Tosylate Would Be Likely to Exhibit Polymorphism	96
(ii)	A POSA Would Have Been Motivated to Search for Polymorphs	99
(iii)	Regulatory and Industry Realities	102
(iv)	Need to Understand the Energy Landscape	107
(v)	A POSA Would Have Been Specifically Motivated to Use Thermal Evaluation Techniques	109
(a)	Melting point	112
(b)	Hot-Stage Microscopy	112
(c)	Differential Scanning Calorimetry (“DSC”)	113
(d)	Thermogravimetric Analysis (“TGA”)	114

(vi)	A POSA Would Have Been Specifically Motivated to Conduct a Polymorph Screen and Motivated to Identify the Most Stable Polymorph.....	114
(vii)	Solution-Mediated Transformations and “Slurrying”	120
(viii)	A POSA Would Have Been Motivated to Run a Standard Solvent Screen	123
D.	A POSA Would Have Had a Reasonable Expectation of Success in Identifying the Most Stable Polymorphic Form of Sorafenib Tosylate.....	124
XIII.	CLAIMS 1-2 AND 28-29 ARE INVALID AS OBVIOUS.....	125
1.	Claims 1-2 and 28-29	126
XIV.	CLAIMS 1-2 AND 28-29 ARE INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING	126
XV.	LACK OF INVENTORSHIP	128
XVI.	SUPPLEMENTAL OPINIONS.....	129

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

I. INTRODUCTION

1. I have been asked by Defendant Mylan Pharmaceuticals, Inc. to provide my expert opinion regarding the validity of the claims of U.S. Patent No. 8,877,933. As explained below, it is my opinion that claims 1-2 and 28-29 are invalid for anticipation, obviousness and obviousness-type double patenting. It is also my opinion that neither named inventor is a true inventor of the claimed subject matter of the patent.

II. QUALIFICATIONS AND EXPERIENCE

2. My curriculum vitae describes my educational background and experience, my technical expertise, and my publications. A copy of my curriculum vitae is attached as Exhibit A.

3. I earned my Ph.D. in organic chemistry from Yale University in 1986. My dissertation, which focused on reactions in organic crystals, was awarded several honors, including the 1986 Wolfgang Memorial Prize (best chemistry dissertation at Yale), the 1987 Nobel Laureate Signature Award for Graduate Education in Chemistry from the American Chemical Society (best chemistry dissertation in the U.S.), and the Distinguished Dissertation Award from the Northeastern Association of Graduate Schools (most distinguished dissertation in physical sciences and engineering from 1983-1987 in a consortium of approximately 60 graduate schools in the northeastern United States).

4. From November 1985 until August 1987, I conducted postdoctoral research at the University of Cambridge. My work focused on solid-state photochemistry, emphasizing the structural and dynamic characterization of reactive intermediates generated from organic molecules trapped in zeolites and organic inclusion compounds.

5. After completing my postdoctoral work, I began my independent academic career in 1987 as an Assistant Professor in the Chemistry Department at the University of Alberta in Edmonton, Alberta, Canada. From September 1991 until August 1998, I was an Assistant

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Professor in the Chemistry Department at Indiana University in Bloomington, Indiana. Between 1991 and 1993, I was a Fellow of the Alfred P. Sloan Foundation. Currently, I am an Associate Professor in the Chemistry Department of Kansas State University in Manhattan, Kansas, a position I have held since 1998. In addition, I have been a Visiting Professor in the Department of Physics at University of Rennes in France, ten times between 2001 and 2014, and I was a Visiting Professor in the Department of Chemistry at the University of Bordeaux, also in France, in 2006.

6. My research has focused on the following areas: (a) processes to isolate organic compounds in the solid state; (b) analytical techniques for characterizing organic solids and the processes that occur within them; (c) solid-state chemistry (broadly defined as the study of various solid forms of chemical compounds); and (d) mechanistic studies of crystal growth and polymorphism, including the effect of solvent used. Throughout my career, my group members and I have used organic synthesis to prepare the compounds that we study in the solid state, including methods for isolation and purification such as crystallization, filtration, washing, and drying.

7. During the course of my work, I have used a variety of techniques to analyze the forms of crystalline materials. These include, but are not limited to, infrared and Raman spectroscopy, melting point, X-ray diffraction (single crystal and powder), differential scanning calorimetry (“DSC”), thermogravimetric analysis (“TGA”), optical microscopy (including birefringence mapping), and solid-state and solution phase nuclear magnetic resonance (“NMR”). During my career, I have personally prepared, reviewed, and analyzed thousands of powder X-ray diffractograms.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

8. During my academic career, I have taught more than 20 different undergraduate and graduate courses. As a professor of organic chemistry, I have taught the theory and practice of crystallization of organic compounds in numerous undergraduate laboratory courses. In addition, I teach the section that deals with the mechanistic aspects of crystal growth of organic compounds in our graduate course in Materials Chemistry. I have supervised the research of 25 Masters, Ph.D., and postdoctoral students. Much of this research includes the study and isolation of particular crystal forms (polymorphs).

9. I have published extensively in the field of crystalline organic materials in peer-reviewed journals, including articles and book chapters as well as meeting presentations dealing with the isolation of new crystal forms, development of processes to obtain these forms, characterization of these solid forms, and chemical and physical processes that occur in crystalline materials. This list of publications includes seven in *Science* and *Nature*.

10. I have been a peer reviewer for a wide variety of journals, including *Science*, *Nature*, *Nature Chemistry*, the *Journal of the American Chemical Society*, *Angewandte Chemie*, *Advanced Functional Materials*, the *Journal of Pharmaceutical Sciences*, the *Journal of Organic Chemistry*, *Crystal Growth and Design*, *CrystEngComm*, *Chemistry of Materials*, and *Molecular Pharmaceutics*. I have been a guest co-editor for special issues of *Molecular Crystals and Liquid Crystals*, *Chemistry of Materials*, and *Crystal Growth and Design*.

11. During the previous 4 years, I have testified as an expert at trial or by deposition in the following cases:

(a) *Cephalon, Inc. v. Agila Specialties Inc. and Onco Therapies Ltd.*, Case No. 1:13-cv-02080-GMS (D. Del.)

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

- (b) *Janssen Pharmaceuticals, Inc. and Gruenenthal GMBH v. Actavis Elizabeth, LLC*, et al. Case No. 2:13-cv-04507-CCC-JAD (D.N.J.)
- (c) *Eisai Co., Ltd., et al. v. Lupin Ltd., et al.* Case No. 1:13-cv-01279-LPS) (D. Del.) (cons.)
- (d) *Shire Development LLC, et al. v. Cadila Healthcare Limited, et al.*, Case No. 1:10-cv-00581-KAJ (D. Del).
- (e) *Genentech, Inc. et al. v. Sandoz, Inc.*, Case No. 3:11-cv-01925-JSW (N.D. Cal.);
- (f) *Celgene Corp. v. Natco Pharma Ltd.*, Case No. 2:10-cv-05197-SDW-LDW (D.N.J.); and
- (g) *Bristol-Myers Squibb Co., et al, v. Mylan Pharmaceuticals Inc.*, et al. Civil Action No. 1:09-cv-00651-LPS (D. Del.)

12. I am being compensated at my standard rate of \$500 per hour. My compensation is not dependent on the outcome of this litigation.

13. The materials I have considered in forming my opinion, in addition to those described in this report, are attached as Exhibit B.

III. SUMMARY OF OPINIONS

14. As explained below, it is my opinion that Claims 1-2 and 28-29 of the '933 patent are invalid on at least the following bases:

- Anticipation because the “general standard method” used Example 1 produces Polymorph I, and even if it did not, any solid form analyzed by conventional thermal techniques (e.g. DSC) would transform into Polymorph I.
- Obviousness for the same reasons as Anticipation, and because conventional polymorph screening techniques (such as slurrying) would have inevitably produced Polymorph I.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

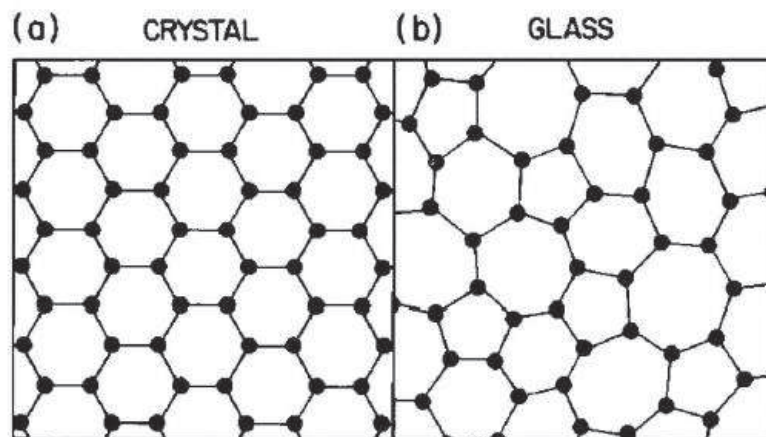
- Obviousness-type double patenting (including the “anticipation” type) over earlier-expiring claims directed to sorafenib tosylate and its use to treat disease states in humans; and
- Lack of inventorship, because neither Dr. Grunenberg nor Dr. Lenz were the first to conceive of sorafenib tosylate Polymorph I or a method of making it.

IV. BACKGROUND

A. Crystals, Crystal Forms, and Polymorphs



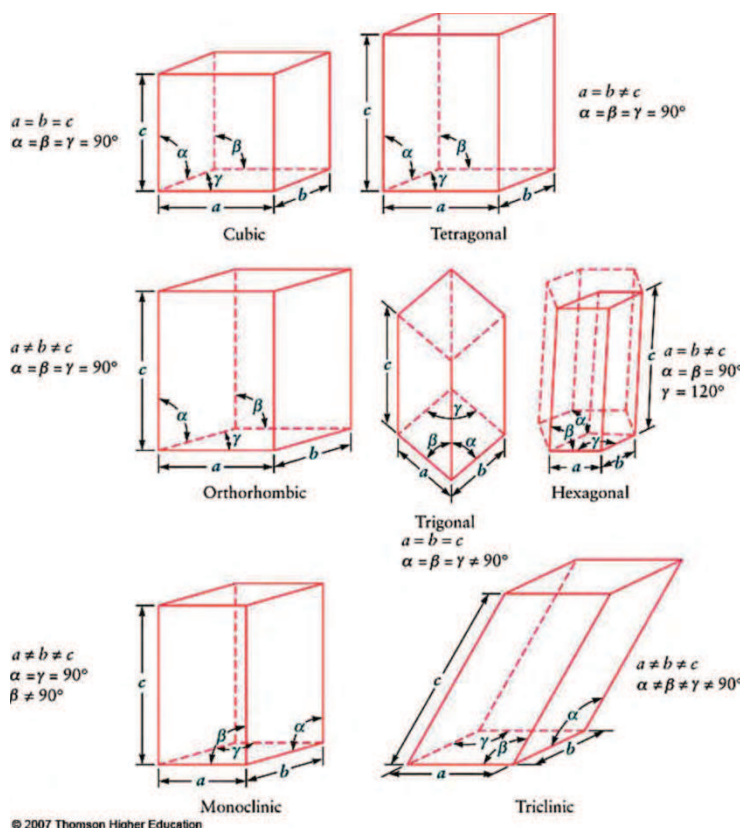
15. A crystal (*e.g.*, quartz) is a solid in which the individual molecules (or atoms) are arranged or packed in a regularly repeating three-dimensional pattern with long-range order. In contrast, an amorphous solid form (sometimes called a “glass”) has considerable disorder in its structure and lacks the long-range order of a crystalline material. Schematic diagrams of the atomic arrangements within a crystalline solid (“a”) and an amorphous solid (here a glass) (“b”) are illustrated below. *See* Richard Zallen, *The Physics of Amorphous Solids*, John Wiley & Sons, New York (1983) at 12.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

16. The smallest repeating unit in a crystalline structure is the “unit cell,” which is the fundamental building block of that crystalline material. The unit cell is essentially a box with a specific size and shape that contains a particular number of molecules in a well-defined arrangement. (For example, a brick wall can be described by the shape and orientation of a single brick. This smallest volume element is called a unit cell.) The dimensions of the unit cell are described by three axes: a , b , c , and the angles between them α , β , and γ . Therefore, the unit cell, as well as the arrangement of atoms within it, is the defining characteristic of a given crystalline form.¹

17. There are seven major symmetry classes of unit cells for crystals as shown below: triclinic, monoclinic, orthorhombic, tetragonal, hexagonal, trigonal (or rhombohedral), and cubic. The most commonly occurring symmetry types in pharmaceuticals are triclinic, monoclinic, and orthorhombic.

¹ See, e.g., Stephen S. Zumdahl, “An Introduction to Structures and Types of Solids,” Ch. 10.3 in *Chemistry*, D.C. Heath and Company, Lexington, MA (1986) at 390-93 (“Zumdahl (1986)”).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

18. The unit cell dimensions for a particular crystal form can usually be obtained through solid-state analytical techniques such as X-ray diffraction. Depending on the symmetry class of the crystal, there may or may not be restrictions on the values of a , b , c , α , β , and γ .²

19. More than one crystalline form of a chemical compound may exist. Crystal forms can be described as “the various types of crystalline solids of the same compound that can be obtained (*i.e.*, polymorphs and pseudopolymorphs); synonymous with crystal modification.”³

20. Different crystal forms with the same chemical composition are called polymorphs, and such compounds are said to exhibit polymorphism. Bernstein follows McCrone in defining a polymorph (a type of crystal form) as “a solid crystalline phase of a given

² See, *e.g.*, *id.* at 391-93.

³ See Stephen R. Byrn, *et al.*, *Solid State Chemistry of Drugs*, 2nd ed., SSCI, Inc., West Lafayette, IN (1999) at 507 (“Byrn (1999)”).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

compound resulting from the possibility of at least two different arrangements of the molecules of that compound in the solid state.”⁴ These definitions make it clear that crystal forms are physical entities with definable chemical and physical properties.

21. Crystalline forms of a given compound may also include solvent molecules within their three-dimensional structures. In general, these forms are called “solvates,” but when the solvent is water, these are called “hydrates.”⁵ A crystal that is not a solvate is often called an “anhydrate” even if there are no known hydrated forms. Solvates are to be distinguished from crystals that simply contain solvent molecules trapped adventitiously in pockets or voids. For any particular compound, there may be a number of different crystalline forms that contain different amounts and/or kinds of solvent within them (“pseudopolymorphs”). There may also be polymorphs of solvates of a given composition.

22. In many instances different crystal forms are related to each other and can convert from one form to another depending upon environmental conditions.

23. Polymorphs or pseudopolymorphs of a given compound are generally given formal names using sequential Roman numerals, Arabic numerals, or letters. The sequence of these numerals or letters may refer to the sequence of phases that occur as a function of temperature or pressure, for example. However, in the pharmaceutical industry, the sequence of numbers or letters normally reflects the sequence of discovery of the different forms.⁶ For example, one of ordinary skill in the art would understand that “Form 1” is the designation given

⁴ See Joel Bernstein, *Polymorphism in Molecular Crystals*, Clarendon Press, Oxford (2002) at 2.

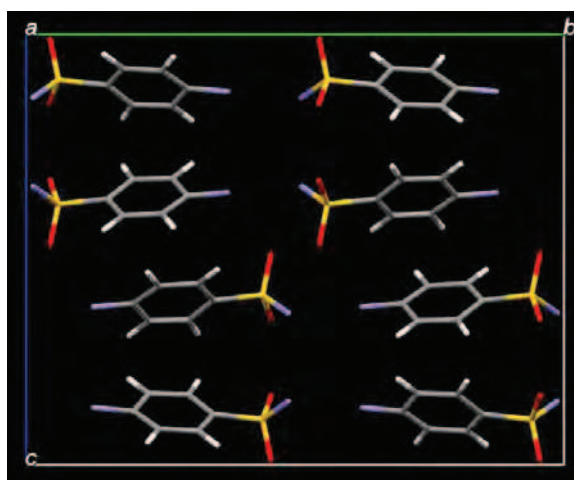
⁵ See, e.g., Guillory, “Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids,” Chapter 5 in *Polymorphism in Pharmaceutical Solids*, H. G. Brittain, Ed., Marcel-Dekker, New York (1999) at 202-205. See also Threlfall (1995) at 2436-2437.

⁶ See, e.g., Terence L. Threlfall, “Analysis of Organic Polymorphs, A Review,” *Analyst*, 120, 2435-2460 (1995) at 2435 (“Threllfall (1995)”).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

to the first crystalline polymorph discovered for a certain chemical entity, “Form 2” is the second, and so on. Each “Form x ” designation refers to a specific, unique crystalline form with its own physical and analytical characteristics.

24. Polymorphs of a chemical substance have different arrangements and/or different conformations of the molecules in the regular repeating pattern of the crystalline lattice.⁷ As an example, the different molecular packing arrangements of three polymorphs of sulfanilamide are shown below.⁸

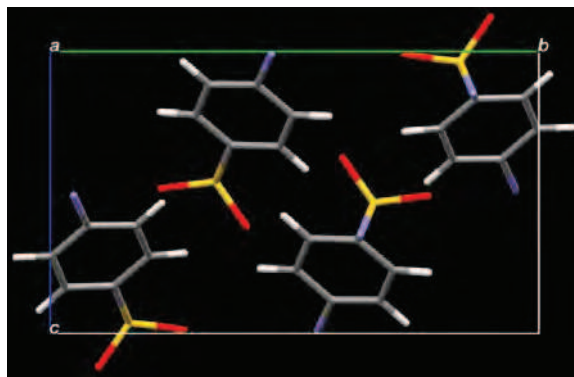


Crystal packing of the α form of sulfanilamide (B. H. O'Connor, E. N. Maslen, *Acta Crystallogr.*, 18, 363 (1965); CSD Refcode SULAMD).

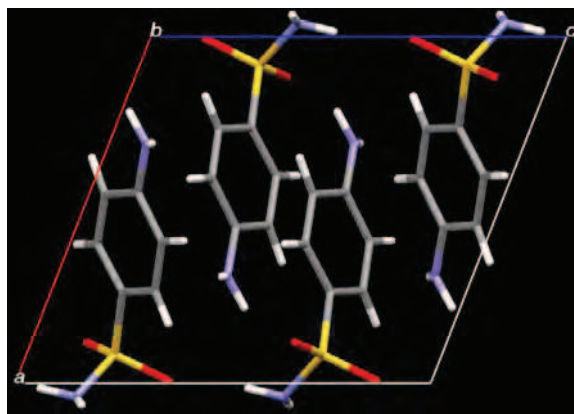
⁷ . See David. J. W. Grant, “Theory and Origin of Polymorphism,” Ch. 1 in *Polymorphism in Pharmaceutical Solids*, H. G. Brittain, Ed., Marcel-Dekker, New York (1999) at 2.

⁸ B. H. O'Connor, E. N. Maslen, *Acta Crystallogr.*, 18, 363-366 (1965); M. Alleaume, J. Decap, *Acta Crystallogr.*, 19, 934-938 (1965); A. M. O'Connell, E. N. Maslen, *Acta Crystallogr.*, 22, 134-145 (1967)

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER



Crystal packing of the β form of sulfanilamide (M. Alleaume, J. Decap, *Acta Crystallogr.*, 19, 934 (1965); CSD Refcode SULAMD02).



Crystal packing of the γ form of sulfanilamide (A. M. O'Connell, E. N. Maslen, *Acta Crystallogr.*, 22, 134 (1967); CSD Refcode SULAMD03).

25. There are numerous analytical techniques for studying and characterizing polymorphs. These include X-ray diffraction, melting point determination, hot-stage microscopy, thermogravimetric analysis, and differential scanning calorimetry. I discuss X-ray diffraction, melting point determination, thermogravimetry, and differential scanning calorimetry below, and I am prepared and able to discuss each of the other techniques mentioned if asked to do so at trial.

B. Thermogravimetric Analysis (“TGA”)

26. In a thermogravimetric analysis (or thermogravimetry), the mass of a compound is monitored as a function of temperature. Typically, a known amount of sample is heated at a

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

constant rate, and the loss of mass due to decomposition or evaporation is recorded as a function of time while an inert gas is flowed past the sample. Both the mass of the sample and the first derivative (mass loss per temperature unit) are plotted as a function of temperature. This is an extremely sensitive method for determining if a crystalline form is a solvate. In particular, the temperature of solvent loss can be used to distinguish bound solvent (as in a solvate) from solvent that is either adhering to the crystal or occurring in liquid pockets or inclusions.

C. Thermal Properties

27. A phase transformation is a process in which there is a physical transformation in the state of material, *e.g.*, liquid to solid or gas to liquid. It can also refer to a transformation between one solid-state form and another. These solid-solid phase transformations are often called phase transitions.

28. In addition to their structural differences, different crystal forms, in general, have different physical properties such as melting points and densities.⁹ With regard to the thermal properties of substances, a good example is water, which can undergo a number of phase transitions. For example, ice can melt to give water, which, in turn can evaporate or boil to give gaseous water or water vapor. Each of these occurs at a characteristic temperature and with a characteristic enthalpy, which is a measure of thermal energy. For melting or boiling to occur, the sample must absorb heat from its surroundings, so these phase transitions are termed “endothermic.” By the same token, when water vapor is cooled, it condenses to give liquid water, which can ultimately crystallize to give ice. These transitions are “exothermic” since water gives off heat to its surroundings in the process.

⁹ *See, e.g.*, Grant (1999) at 5-8.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

D. Melting Point

29. It should be clear then, that one method of characterizing crystal forms is by taking a melting point. The presence of a reasonably sharp melting point is a useful way of telling if an organic solid is crystalline as opposed to amorphous. An amorphous solid has a glass transition temperature, not a melting point, which signals a discontinuous phase change to the liquid state.

30. It is often possible to distinguish two polymorphic forms by their melting points, especially when the melting points are well separated. In certain cases, however, this is not possible because a solid-solid phase transition converts one polymorph into another one prior to melting of the second form. In such cases, only one melting point is observed, even though the system is polymorphic.

E. Differential Scanning Calorimetry (“DSC”)

31. Differential Scanning Calorimetry (“DSC”) is a type of test that can be used to measure the melting point of a material. DSC uses the thermal characteristics of different phase transitions to distinguish between different materials. In DSC, one applies enough thermal energy (or power) to the sample and a reference to keep them at the same temperature while warming or cooling. The DSC data is in the form of a curve showing the heat flow as a function of sample temperature. The direction of the peak (which is either endothermic or exothermic) helps to identify the type of transformation taking place. Different calorimeter manufacturers use different conventions for displaying the direction of heat flow. With some instruments, endothermic transitions give a displacement of the DSC curve along the positive y-axis. In others, endothermic transitions appear as negative peaks.

32. The DSC trace complements the melting point by providing detailed information about the melting transition, including the enthalpy of fusion (*i.e.*, the heat energy that must be

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

added to melt a specific amount of the substance), which is a characteristic property of each crystalline form. The DSC can provide diagnostic information related to pre-melting behavior, phase transitions, decomplexation of bound solvent, eutectic mixtures (discussed below in section M), and chemical decomposition.

33. In particular, DSC is used throughout the pharmaceutical industry to identify new crystalline forms of drug substances. Both desolvation and solid-solid phase transformations give rise to signals in the DSC trace and would prompt further investigation of the crystal forms generated by these thermal processes.

F. Powder X-ray Diffraction (“PXRD”)

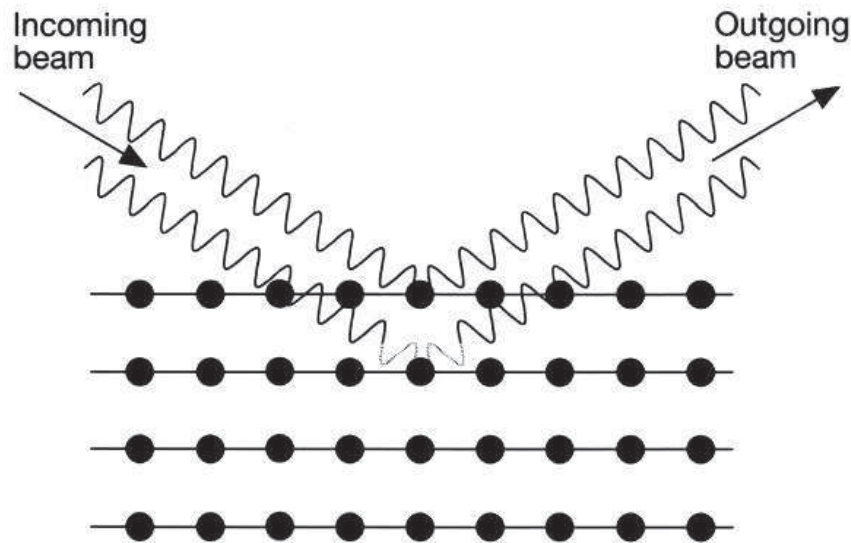
34. X-ray diffraction is a common analytical technique that relies on the scattering patterns caused by different objects when exposed to X-rays. PXRD is one of the most commonly used techniques for characterizing crystalline polymorphs. Each different crystal structure has a unique pattern of scattered radiation, called a diffraction pattern. When an X-ray beam hits an atom, the electrons around the atom start to oscillate with the same frequency as the incoming beam. As a result of this process, the X-rays are scattered in all directions by the atoms. Because of the wave character of the X-rays, the scattered radiation from different atoms can interfere either constructively or destructively. (That is, the scattered waves from sets of atoms can be either in phase or out of phase with each other.)¹⁰

35. In most directions, there is destructive interference, meaning that the combining waves are out of phase, and, therefore, no signal can be observed by a detector at that orientation. However, because the atoms in a crystal structure or lattice are arranged in a regular, repeating

¹⁰ See Zumdahl (1986) at 391-93.

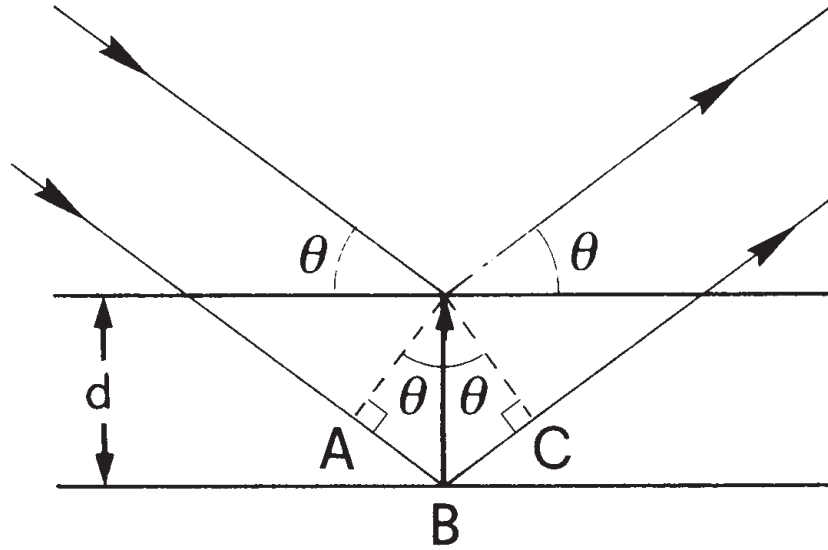
HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

pattern, in certain directions, constructive interference results when the X-rays are diffracted, as shown below.



36. Thus, for a single crystal exposed to monochromatic X-rays (*i.e.*, X-rays of a single wavelength), diffraction will be observable for certain values of the angle of incidence (theta or θ , as depicted in the diagram below). This relationship is described by Bragg's law, as explained in the following paragraph.¹¹ Another figure showing this principle appears below.

¹¹ See Ron Jenkins and Robert L. Snyder, "Diffraction Theory," Chapter 3 in *Introduction to X-ray Powder Diffractometry*, John Wiley & Sons, Inc., New York, NY (1996) at 47-63 ("Jenkins & Snyder (1996)").

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

37. Bragg's Law uses the following formula for interconverting 2θ values and d -spacings:

$$n\lambda = 2d \sin \theta$$

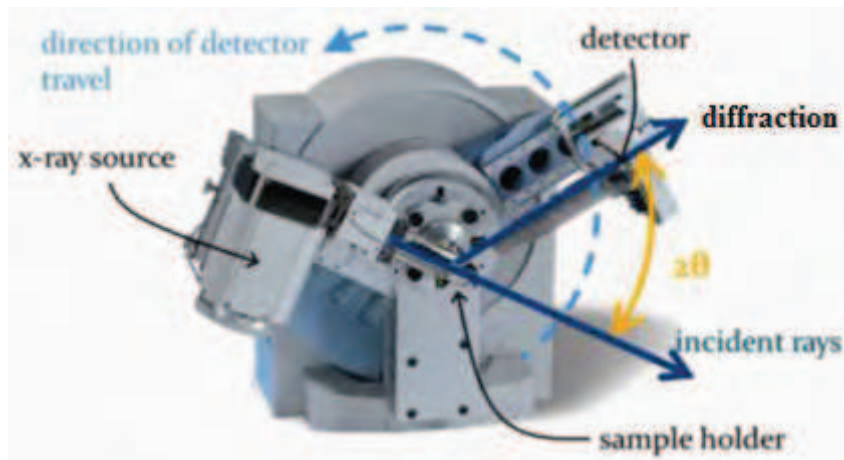
where n is an integer determined by the order of the diffraction (generally, $n = 1$), λ is the wavelength of the incident wave (*e.g.*, for diffractometers using copper K alpha radiation ($\text{CuK}\alpha$), $\lambda = 1.54178 \text{ \AA}$), d is the spacing between the planes in the crystal lattice (in Angstroms, discussed further below), and θ is one-half of 2θ , which is the angle between the incident X-ray beam and the diffracted X-rays.¹²

38. The instrument used for X-ray diffraction is called an X-ray diffractometer, which consists of three basic elements: an X-ray tube, a sample holder and an X-ray detector. The sample being investigated is placed under an intense beam of X-rays, usually of a single wavelength (monochromatic X-rays), resulting in a detectable X-ray diffraction pattern. Specifically, by changing the geometry of the incident X-rays, the orientation of the sample, and

¹² See Zumdahl (1986) at 393.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

that of the detector, a range of possible diffraction directions from the crystal is obtained. Thus, each positioning produces a different X-ray diffraction intensity.¹³



39. All X-ray diffraction techniques are based on generation of X-rays. X-rays are typically generated in an X-ray tube by applying a voltage through a filament to produce electrons that are accelerated towards a metal target (*e.g.*, copper (“Cu”)). When there is sufficient energy to dislodge electrons from the metal target, characteristic X-ray radiation is produced that consists of several components, each of which is given a name that corresponds to the particular electronic transition. Two of the major classes of transitions are the K_{α} and K_{β} transitions. K_{α} transitions can be broken down further into $K_{\alpha 1}$ and $K_{\alpha 2}$ transitions, where $K_{\alpha 1}$ ($\lambda = 1.54056 \text{ \AA}$ for Cu) has a slightly shorter wavelength than $K_{\alpha 2}$ ($\lambda = 1.54443 \text{ \AA}$ for Cu).¹⁴ By passing the X-rays through a monochromator, one can all but eliminate the K_{β} transitions to leave only the K_{α} transitions. However, since $K_{\alpha 1}$ and $K_{\alpha 2}$ are sufficiently close, both wavelengths may pass through the monochromator, and the weighted average of the two wavelengths ($\lambda = 1.54178 \text{ \AA}$) may be used, especially at lower angles. With certain monochromators and/or a software filtering routine called “ $K_{\alpha 2}$ stripping,” it is more appropriate

¹³ See Jenkins & Snyder (1996) at 47-95.

¹⁴ See Jenkins & Snyder (1996) at 389.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

to use the value of $K_{\alpha 1}$ ($\lambda = 1.54056 \text{ \AA}$). The use of different monochromators will have a slight impact on the observed location of peaks in the diffraction pattern, but this can be calculated if the effective wavelengths are known.

40. For *single crystal X-ray diffraction*, the first step is the selection of a single crystal using a microscope. Polarized light microscopy is an analytical technique that provides a rapid method of studying polymorphism by observing the homogeneity or diversity of crystalline samples. This technique also offers the opportunity to further characterize a single crystal by allowing the selection of one crystal under the microscope. Following selection of a single crystal, the diffraction intensity data is recorded. Once the unit cell is determined, single crystal X-ray crystallography techniques are employed to determine three-dimensional details (*i.e.*, atomic coordinates) of the molecule as well as the packing of the molecule within the single crystal.¹⁵

41. *Powder X-ray diffraction* (PXRD or XRPD) does not require large single crystals but instead can be applied to powdered samples.¹⁶ This is a widely used technique because most materials are not single crystals and are instead composed of tiny crystallites (or microcrystals). When a powder containing randomly oriented crystals is placed in an X-ray beam, the intensities of the diffracted X-rays are recorded to produce a diffraction pattern. The X-ray diffraction pattern is thus a plot of the diffraction intensities (*i.e.*, intensity of the diffracted X-ray beam) as a function of 2-theta values (*i.e.*, 2θ , twice the angle of incidence) and may be considered a “fingerprint” of the particular polymorph crystal being examined.¹⁷

¹⁵ See, *e.g.*, Threlfall (1995) at 2445-46.

¹⁶ See Jenkins & Snyder (1996) at 58-60.

¹⁷ See Jenkins & Snyder (1996) at 47-74.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

42. To see how the PXRD pattern for a given crystal form is a “fingerprint” that is an inherent property of that crystal form, it is first necessary to note, as stated above, that all crystal forms are defined by their unit cells, which are the fundamental repeating units within the crystal structure. The unit cell—whose size and shape is described by the cell lengths, a , b , c , and the angles between them α , β , and γ —may be sliced in specific ways into a set of parallel planes, called Miller planes, in which the separation between planes is some fraction of each of the unit cell edges. The separation between these Miller planes defines the d-spacings (*i.e.*, lattice spacings between parallel planes) that are allowed for a given crystal structure. In powder X-ray diffraction, each of the peaks corresponds to a family of atomic planes or “Miller planes” in the crystal structure, each with its own d-spacing. Because the PXRD pattern for a given form is characterized by its d-spacings (or corresponding 2θ values), which are also defined by the unit cell, the set of d-spacings (or corresponding 2θ values) observed in the PXRD pattern is an intrinsic property of any given crystal form.

43. In powder X-ray diffraction, the observed intensities are due to the contents of the unit cells and the arrangement of the atoms within each cell. Although subject to more variability than 2θ values or d-spacings, the observed intensities are also inherent properties of the crystal structure (the unit cell, its contents, and the arrangement of atoms within it) and are therefore inherent properties of a given crystal form. As discussed below, the crystal structure may be used to calculate the two-dimensional X-ray diffraction pattern to be expected from a powder of the same material. This calculated powder X-ray diffraction pattern would be unencumbered by impurities, including the presence of other polymorphs.

44. Even without a three-dimensional crystal structure, the unit cell and space group (*i.e.*, symmetry type) can be used to calculate all of the peak positions that might possibly be

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

observed in a powder X-ray diffractogram of the given material, but this calculation provides no information about the intensities of such peaks (including whether or not they would be observed).

45. To give a signal in a diffractometer using a reflecting geometry, a given Miller plane, as defined above, must lie horizontally in the plane of the sample holder, and the 2θ value must fulfill the conditions of Bragg's Law for the corresponding d-spacing, as explained with respect to the equation above. In this method, each crystallite has a certain orientation that may or may not meet the Bragg condition for diffraction at a given angle. To ensure that the crystallites are oriented randomly throughout the sample, the polycrystalline sample should contain a multitude of crystallites.¹⁸

46. As explained above, in order to obtain an accurate PXRD pattern, the crystals in a powder should have random orientations. If the orientations of the crystallites are not random, certain peaks will be overrepresented compared to other peaks, and the intensities of certain peaks may be skewed. Because many peaks in a PXRD pattern are actually the superposition of two or more peaks, the enhanced or attenuated intensity of a given peak component can give rise to small shifts in the observed peak position. A sample having non-random orientation of crystals in a powder is referred to as having "preferred orientation." Preferred orientation can be minimized or eliminated through the use of routine sample preparation techniques.

47. Preferred orientation can be reduced in several ways, including packing the sample more appropriately, light grinding of a sample, or rotating the sample as it is being tested to change the orientation of the sample with respect to the X-ray beam (thus creating a more random orientation of the crystals as diffraction of the X-rays is measured).

¹⁸ Jenkins & Snyder (1996) at 47-95.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER**G. Calculated PXRD Pattern Based on Single Crystal Data**

48. For virtually any crystalline material, once the single crystal structure of the material is determined, it is possible to calculate a theoretical diffraction pattern. For a given X-ray wavelength (*e.g.*, Cu K α) this calculation provides the complete PXRD pattern, including both intensities and 2θ values for each and every peak that is possible for the given crystal structure. It also provides the crystallographic indices (*i.e.*, lattice planes) for all of the peaks in the PXRD pattern. Because the calculation of the theoretical PXRD pattern assumes random orientation for the crystallites in the sample, this theoretical pattern does not exhibit “preferred orientation,” which can affect the intensities in an experimental pattern. However, it is possible to include a preferred orientation parameter that corrects for the non-ideal distribution of crystallite orientations in the sample.

49. Calculation of the theoretical PXRD pattern from the crystal structure¹⁹ is a straightforward process that takes less than a second. Indeed, software to generate the PXRD pattern from single crystal data has been widely available since at least 1992. With the CERIUSTM software program (from Molecular Simulations, Inc.), which has been widely available since 1992, calculation of the PXRD pattern from a known crystal structure can be accomplished by simply pressing a button in the graphical user interface. The manual states:

CERIUS Diffraction I simulates the crystal diffraction patterns of models built in the CERIUS Crystals facility or loaded from stored files.

...

It is simple to use, since the diffraction pattern of the current model may be calculated and displayed at any time *merely by pressing a button on the GUI.*²⁰

¹⁹ Jenkins & Snyder (1996) at 75-85.

²⁰ CERIUS Manual (Molecular Simulations, Inc., Dec. 1992) (emphasis added).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

50. To accomplish this task, many scientists use the program Mercury, which, in addition to the Cambridge Structural Database (CSD), is distributed by the Cambridge Crystallographic Data Centre (CCDC). Since this process is so straightforward, calculation of the theoretical PXRD pattern and comparison of this calculated pattern with an experimental pattern is an essential tool that is used routinely by a person of ordinary skill in the art.²¹

51. Generation of the PXRD pattern from the single crystal data allows a much more detailed assessment of the experimental PXRD pattern from bulk material because each peak in the experimental pattern is already indexed by the crystal structure file. This immediately provides information about whether or not an experimental pattern is influenced by preferred orientation and whether or not it fits the theoretical pattern.

52. One important advantage of calculating a theoretical PXRD pattern for a given crystal form is that it is possible to identify peaks in an experimental PXRD pattern that cannot belong to the particular form whose complete crystal structure has been determined from single crystal diffraction. If the experimental pattern contains a peak at a position where there is no intensity in the theoretical pattern, then this peak, as a matter of science, must arise from something other than the crystal form defined by the crystal structure. Such a peak indicates either that an impurity is present or that the sample as a whole is a different form than the one whose structure has been determined. A simple truth is that a peak cannot be a “characteristic peak” for a particular crystal form if that peak does not exist in the theoretical pattern for that form.

53. The Mercury program uses the unit cell, atomic coordinates, and space group symmetry to calculate the theoretical PXRD pattern from the crystal structure. In particular, it

²¹ MERCURY 3.0 Manual, Cambridge Crystallographic Data Centre (2012).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

uses the unit cell dimensions to calculate the peak positions and the atomic coordinates and space group symmetry to calculate the peak intensities. With many high-symmetry space groups, certain peaks are “systematically absent” due to certain symmetry elements in the crystal structure. Such peaks would not appear in the list of calculated peak positions because they are forbidden by symmetry.

H. Hot-stage Microscopy

54. Hot-stage microscopy has been employed for decades in the pharmaceutical industry to assess transitions between crystal forms including solvates and anhydrides. In this method, the sample is heated gradually on a microscope stage while events are recorded visually or with either photographs or videos. This is a convenient technique that allows a scientist to visually observe and record phase changes as a function of temperature. Hot-stage microscopy is often used in conjunction with differential scanning calorimetry (“DSC”).

55. Threlfall recognizes that hot stage microscopy is a technique for generating polymorphs. In particular, he states: “hot-stage microscopy has been often so used and remains the outstanding method for the examination and generation of polymorphs.”²² He further states:

A preliminary examination under a binocular microscope will enable the overall characteristics of the sample to be ascertained. Temperature cycling and melt and solvent recrystallization experiments with a polarizing microscope equipped with a hot-stage will allow the identification of transition points, the distinguishing of monotropic and enantiotropic relationships, estimation of the tendency of melts and individual phases to supercool, *the generation of stable and unstable polymorphs* and the recording of their optical properties. The identification of solvates and the observation of sublimates and of any tendency to decompose are added information. This can be carried out with minute amounts of material. The field has been excellently and

²² Threlfall (1995) at 2439.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

comprehensively reviewed in the past, and for that reason only the developments since then will be considered in detail here.²³

Thus, hot stage microscopy is an important tool for investigating polymorphism of crystalline solids.

I. Infrared Spectroscopy

56. Infrared (IR) spectroscopy is a widely available vibrational spectroscopy technique that is useful for identifying and distinguishing different crystal forms. A transmission-mode infrared spectrum is obtained by comparing the ability of a sample to absorb incident infrared light with that of a reference or blank sample. Vibrations that occur within the sample can absorb infrared radiation when their frequencies match the frequencies of the incident beam.

57. The infrared region of the electromagnetic spectrum may be characterized by three regions, which are named by their proximity to the visible region of the electromagnetic spectrum,

1. Mid-IR region

58. The mid-IR region, which spans from approximately $4000\text{-}400\text{ cm}^{-1}$, corresponds to the energies of molecular vibrations of organic molecules. It is widely used by organic chemists to identify compounds because certain "functional groups" in a molecule absorb infrared radiation in specific regions of the spectrum. For a typical organic compound, the mid-IR region of the spectrum contains numerous absorptions. The infrared spectrum of a given

²³ Threlfall (1995) at 2439 (emphasis added); *see also* Byrn (1999) at 279.; Mino R. Caira, "Crystalline Polymorphism of Organic Compounds," *Topics in Current Chemistry*, 198, 163-208 (1998) at 178 ("Caira (1998)"); John Haleblan and Walter McCrone, "Pharmaceutical Applications of Polymorphism," *Journal of Pharmaceutical Sciences*, 58(8), 911-929 (1969) at 918.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

crystalline form is a diagnostic test that is often used in the pharmaceutical industry to characterize a particular form and to distinguish it from other forms.²⁴ Although many IR peaks are unaffected by the form of the crystalline material, others may change with crystalline form. Thus, certain regions of the IR spectrum are more diagnostic than others for distinguishing crystalline forms.

59. The IR spectrum between 400 and 1500 cm^{-1} is known as the “fingerprint” region. This region is called the “fingerprint region” because each molecule has a different combination of coupled vibrations that give rise to a characteristic spectrum. Because the frequencies in the fingerprint region are sensitive to the conformation (shape) and environment (*i.e.*, adjacent molecules) of a given molecule, different crystal forms of the same compound will typically absorb at different frequencies in this region. For some materials, the high frequency region can also be diagnostic, especially when there are differences in hydrogen bonding between different crystal forms (both polymorphs and pseudopolymorphs).

2. Far-IR (FIR) region

60. The far-IR region of the spectrum occurs at frequencies below 400 cm^{-1} ; although the exact frequency ranges covered by different spectrometers vary, a typical range might be 50 to 200 cm^{-1} . Certain molecular vibrations occur within the far-IR region of the spectrum. However, this region of the spectrum is distinguished from the mid-IR region because it contains low-frequency “lattice vibrations” that require cooperative movements of many molecules in addition to molecular vibrations. Because the intensities and/or frequencies of these lattice

²⁴ Threlfall (1995) at 2438; David E. Bugay, “Characterization of the solid-state: spectroscopic techniques,” *Advanced Drug Delivery Reviews*, 48(1), 43-65 (2001) (“Bugay (2001)”); Bernard Van Eerdenbrugh & Lynne S. Taylor, “Application of mid-IR spectroscopy for the characterization of pharmaceutical systems,” *International Journal of Pharmaceutics*, 417(1-2), 3-16 (2011) (“Van Eerdenbrugh (2011)”).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

vibrations depend on the crystal packing and symmetry of the crystal, far-IR spectroscopy can, in principle, be used to distinguish different crystal forms, including polymorphs and pseudopolymorphs. This method is not widely used, primarily because of the weakness of signals in this region of the spectrum, instrumentation issues, and the availability of Raman spectroscopy (see section K) as an alternative.

3. Near-IR (NIR):

61. The near-IR region of the spectrum spans from $4,000\text{ cm}^{-1}$ to approximately $12,500\text{ cm}^{-1}$. Vibrations observed in this region of the spectrum are either overtones (second harmonics) of molecular vibrations whose fundamental frequencies are in the mid-IR region, or bands that are combinations of either fundamental molecular modes or overtones. Most organic compounds have relatively few absorptions in this region, and they tend to be weaker than in the mid-IR region of the spectrum. This relative transparency is an advantage, however, since it allows the scientist to study thicker samples (such as intact crystallites, which may be too thick to study in the mid-IR region of the spectrum).

J. Raman spectroscopy

62. Raman spectroscopy is a powerful form of vibrational spectroscopy that relies on inelastic scattering of light from either a near-infrared or visible laser instead of absorption (as in infrared spectroscopy). This technique can be used to probe the far-IR, mid-IR or near-IR regions of the spectrum, whose vibrations have characteristics described above. The selection rules for observation of Raman and infrared bands are different, so infrared and Raman spectroscopy are often said to be complementary. Because it relies on inelastic scattering instead of absorption of light, Raman spectroscopy is useful for intact crystals, which are often too thick for transmission infrared spectroscopy. A Raman spectrometer can be attached to a microscope,

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

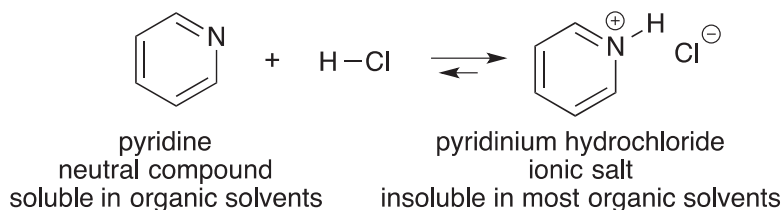
so this allows one to collect Raman spectra on individual crystallites in a sample. This technique is used throughout the pharmaceutical industry to study crystal forms.²⁵

K. Inherent Properties of Physical Forms

63. Properties such as PXRD reflections, IR, NIR and FIR spectral peak maxima, Raman spectra peak maxima, and melting point are inherent properties of a compound in its particular physical form. Any particular physical form will have those properties.

L. Salt Formation

Formation of a salt by acid-base addition is a simple chemical technique that has been taught to undergraduates for many decades. [reference: Ralph R. Shriner, Reynold C. Fuson, David Y. Curtin, and Terence C. Morrill, “The Systematic Identification of Organic Compounds,” 6th Ed. pp. 90-94, 104 (1980).] Many pharmaceutical compounds (such as sorafenib) contain basic groups that will react with strong acids to form ionic salts. This can have a dramatic effect on the solubility of a compound in organic solvents (such as ethanol). For example, as shown below, the reaction of pyridine, a neutral organic base, with hydrochloric acid, produces an ionic salt known as pyridinium hydrochloride. (The small arrow in the reverse direction indicates that the equilibrium lies far to the right and that only a tiny fraction of pyridine and hydrochloric acid remain unreacted.)



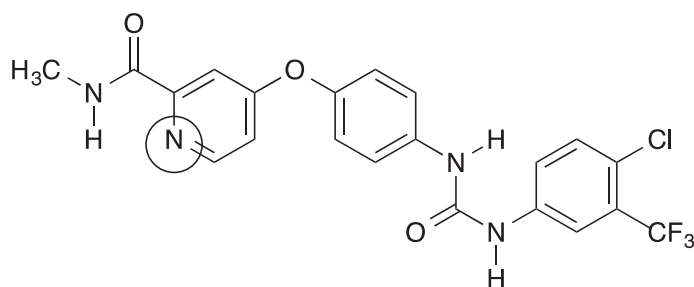
²⁵Threlfall (1995) at 2438; Bugay (2011); T. Vankeirsbilck, et al., “Applications of Raman spectroscopy in pharmaceutical analysis,” *TrAC Trends in Analytical Chemistry*, 21(12), 869-877 (2002).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Although pyridine is soluble in most organic solvents, pyridine hydrochloride is insoluble in these same solvents because of its ionic nature. (Because of their charges, ionic species are attracted to each other very strongly and form stable crystalline structures. Disruption of such stable ionic structures often requires a highly polar solvent such as water.)

In general, “like dissolves like,” so a substance that is neutral will dissolve in organic solvents that are neutral. An ionic salt (such as pyridinium hydrochloride), on the other hand, will precipitate from an organic solvent as it is formed in acid-base reactions such as the one shown above.

The free base of sorafenib acts much like pyridine in the example above. Because it is a neutral compound, it is soluble in common organic solvents such as ethanol. However, because it contains a pyridine subunit in its structure, it can also react with strong acids, which protonate the pyridyl nitrogen circled in the diagram.

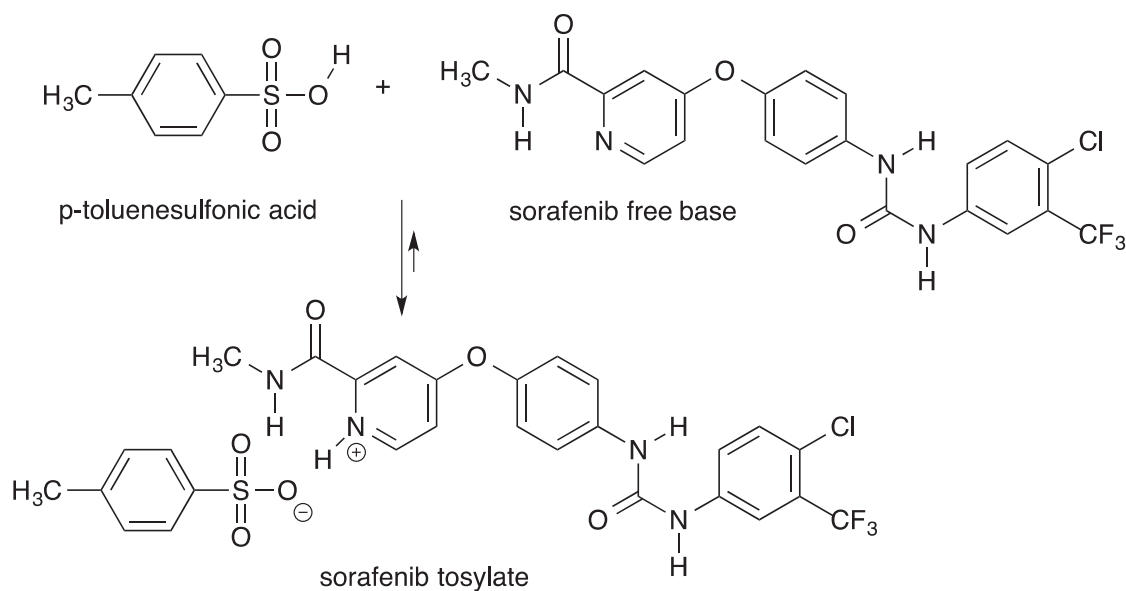


p-Toluenesulfonic acid is a common acid used throughout the pharmaceutical industry to form ionic salts with neutral bases.²⁶ Like hydrochloric acid, it is a strong acid that can react with the pyridyl group in sorafenib free base, as shown in the reaction below. Because it is an

²⁶ Heinrich Stahl & Camille G. Wermuth, Chapter 12 (Monographs on Acids and Bases), in *Handbook of Pharmaceutical Salts*, Heinrich Stahl & Camille G. Wermuth, Eds. Wiley-VCH, 265-327 (2002), at 309-310. (“Stahl (2002)”)

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

ionic salt, the sorafenib tosylate that is formed in this reaction is insoluble in ethanol and therefore precipitates from this solvent.

**M. Mixtures and eutectic points**

64. Frequently, impure materials are encountered in the DSC. On common scenario is congruent melting of a mixture of two materials. “Congruent” melting occurs when the composition of the liquid formed from melting is the same as that of the solid. (This is opposed to “incongruent” melting, where the liquid formed is a different material than the solid, such as with melting by degradation).

65. The simplest case is a mixture of two materials (a binary mixture). Giron discusses the phase diagrams of binary mixture:

Fig. 4 shows some typical phase diagrams of binary mixtures. When manufacturing salts, the possible occurrence of such phase diagrams needs to be considered. Besides the pure compound (*i.e.* the salt), eutectic mixtures of between the acidic and basic components can result. Congruent or incongruent melting of the

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

solvate (or of the salt) may be observed (Fig 4, d and e), leading to a mixture of the two components after melting.

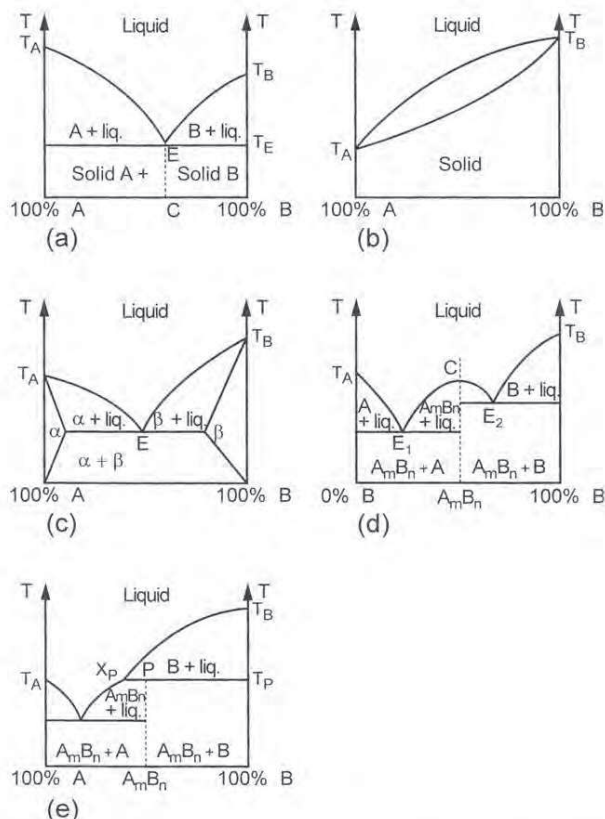


Fig. 4. Phase diagrams of binary mixtures of temperature vs. composition (e.g., mole fraction) of two chemical compounds, A and B, showing the following behavior: a) simple eutectic, with negligible miscibility in the solid state, b) continuous range of solid solutions (miscibility in the solid state as well as in the liquid state), c) eutectic with partial miscibility in the solid state, d) formation of a compound with a congruent melting point at C, e) formation of a compound with an incongruent melting point at P

Danielle Giron and David J. W. Grant, "Evaluation of Solid-State Properties of Salts," in P. Heinrich Stahl & Camille G. Wermuth, Eds., *Handbook of Pharmaceutical Salts*, Wiley-VCH, pp. 41-81 (2002) at 46-47 ("Giron (2002)").

66. In the case of salts, like sorafenib tosylate, it is not uncommon to have unreacted base or acid in the product, creating a binary mixture.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

67. An example of the phase diagram for a binary mixture is given in Figure 1.11 of Storey.²⁷

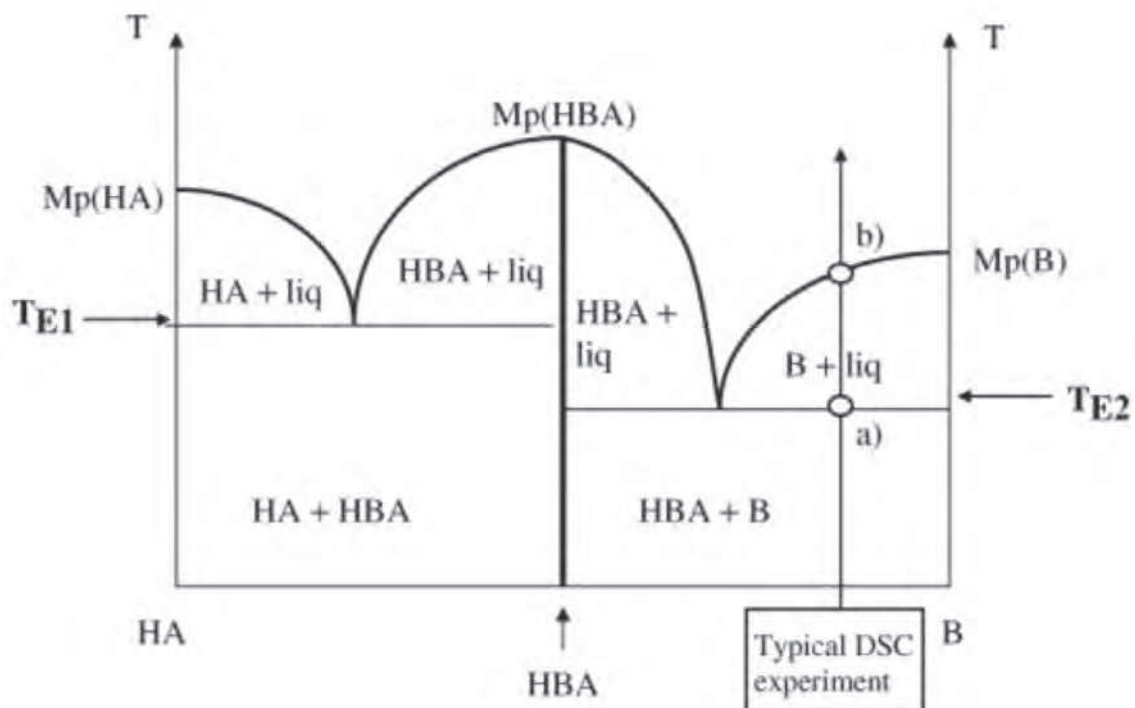


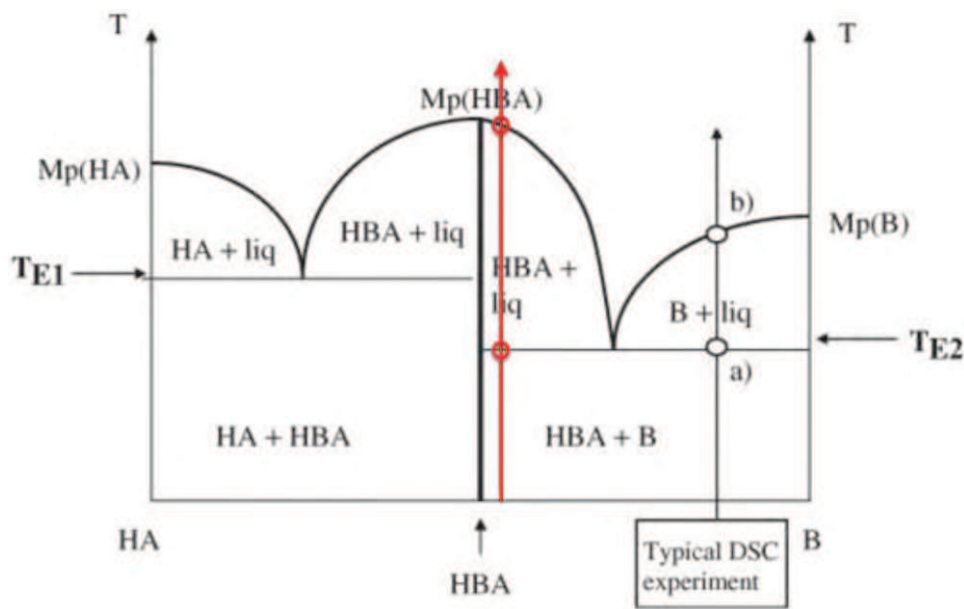
Figure 1.11 shows a two-component phase diagram for a 1:1 salt (denoted as HBA in the figure) and its corresponding crystalline acid and base (denoted HA and B with melting points $Mp(HA)$ and $Mp(B)$ in the figure). The salt forms eutectics with both acid and base (eutectic melting temperatures are denoted $TE1$ and $TE2$ in the figure) and thus has a normal (congruent) melting point denoted as $Mp(HBA)$ in the figure (less common salts with incongruent melting points also appear – Purdon and Slater 1946). There are also two miscibility gaps, denoted HA + HBA and HBA + B. The melting point of the salt is in this case higher than those of the acid and base, but it may just as well be lower. A phase diagram of the type in Figure 1.11 can be obtained using a DSC to study the melting behaviour of various mixtures of HA + HBA and B+HBA. In the right side of the figure the propagation of such a DSC-experiment is shown by an arrow with two circles. The circles show two melting events that will occur in the DSC curve: first the eutectic melting point (at the circle a) and then the final melting (at circle b). From such an experiment the circled data (a)

²⁷ Richard A. Storey (2011-04-08). *Solid State Characterization of Pharmaceuticals* (Kindle Locations 789-801). Wiley. Kindle Edition.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

and (b) are plotted into the figure and after 5–10 such DSC experiments the whole diagram can be drawn. The presence of enantiotropic polymorphs makes the diagram slightly more complicated. If the acid or the base (or both) is polyfunctional, new salts may also appear in the molar positions 1:2, 2:1 and so forth but the system will still remain a two-component system.

In the case of sorafenib tosylate, “HBA” represents sorafenib tosylate in Figure 1.11 of Storey (and in the diagram below), “HA” represents p-toluenesulfonic acid, and “B” represents the free base of sorafenib. In Storey’s Figure 1.11, the heating line showing a “typical” DSC experiment represents a case in which a large amount of free base is present in addition to the salt. In cases in which small amounts of free base are present with the salt, the red line on the diagram below is a better representation of the situation; here, where the composition much closer to a mixture of the salt containing a small amount of free base, the free base melts as a eutectic (below the melting point of the pure free base) to give a mixture of the salt and a liquid above the eutectic (HBA + liq). It is also clear from this phase diagram that in the presence of base, the melting point of HBA (sorafenib tosylate in the present case) is somewhat lower than that of pure HBA.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Once the free base has melted and has formed a liquid in the presence of a salt containing the same base (the “HBA + liq” region of the phase diagram above), the base may react with HBA to form chemical entities other than the original free base, so cooling through $TE2$ may or may not form the original mixture of HBA + B.

V. U.S. PATENT NO. 8,877,933

A. The '933 patent

68. I have been asked to provide my opinion regarding the validity of United States Patent No. 8,877,933 (“the ’933 patent”), titled “Thermodynamically Stable Form Of A Tosylate Salt”. The ’933 patent issued from the United States Patent and Trademark Office (USPTO) on November 4, 2014.

69. The ’933 patent issued from U.S Patent Application No. 11/664,363 (“the ’353 application”), which was the National Stage of Patent Cooperation Treaty Application No. PCT/EP2005/010119 (“the PCT ’119 application”), filed on September 20, 2005. The PCT ’119 application claimed priority to European Application No. EP 04 023 130 (“the EP ’130 application”), filed on September 29, 2004.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

70. The '933 patent names Drs. Alfons Grunenberg and Jana Lenz as inventors (collectively, "the Inventors") and is assigned on its face to Bayer Intellectual Property GmbH.

B. Asserted Claims

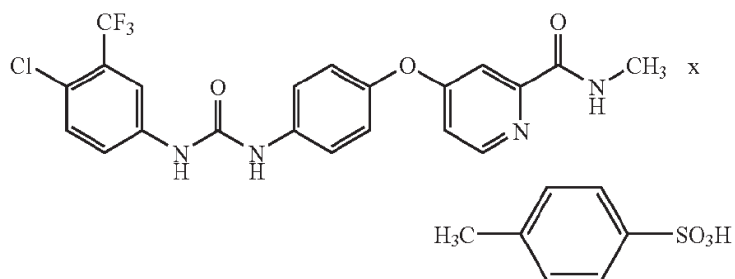
71. The claims of the '933 patent generally relate to Polymorph I of sorafenib tosylate.

72. Plaintiffs have asserted claims 1-2, 8-10, 16, 18-19, 21, 28-29 of the '933 patent.

73. Claims 1-2 are directed to:

Claim 1: A compound of the formula (I)

(I)



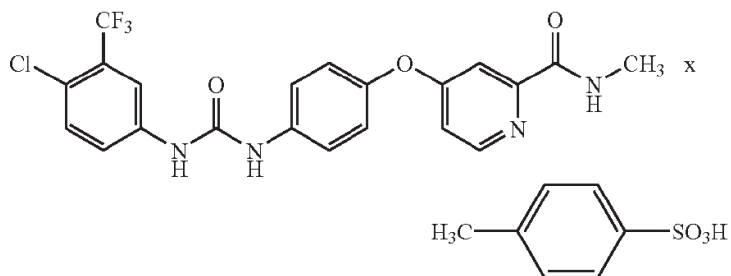
in the polymorph I form, which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5

Claim 2: The compound of claim 1 which shows in the X-ray diffractometry peak maxima of the 2 theta angle comprising 4.4, 14.8, 20.5, 20.8, 21.5 and 22.9.

74. Claims 8-10 are directed to:

Claim 8: A pharmaceutical composition comprising a compound of formula (I):

(I)



substantially in the polymorph I form which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5.

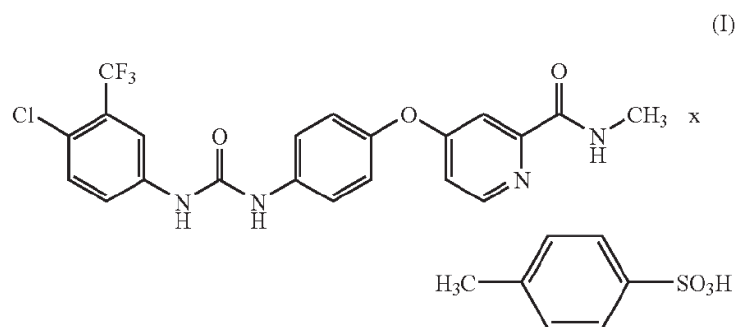
HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Claim 9: The pharmaceutical composition as claimed in claim 8, further comprising one or more inert, nontoxic, pharmaceutically suitable excipients.

Claim 10: The pharmaceutical composition of claim 8, wherein the compound of formula (I) is present in the polymorph I form in the composition in an amount equal to or more than 90 percent by weight of the total weight of the compound of formula (I) present in the composition.

75. Claim 16 is directed to:

A method of treating a disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I)



in the polymorph I form which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5.

76. Claims 18-19 are directed to:

Claim 18: The method of claim 16, wherein the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid gland, kidney or intestine.

Claim 19: A method for treating a disorder, comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of any one of claims 8 to 15.

77. Claim 21 is directed to:

The method of claim 19, wherein the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid gland, kidney or intestine.

78. Claims 28-29 are directed to:

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Claim 28: A compound having the x-ray diffraction pattern of polymorph I in FIG. 2 of the application which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5.

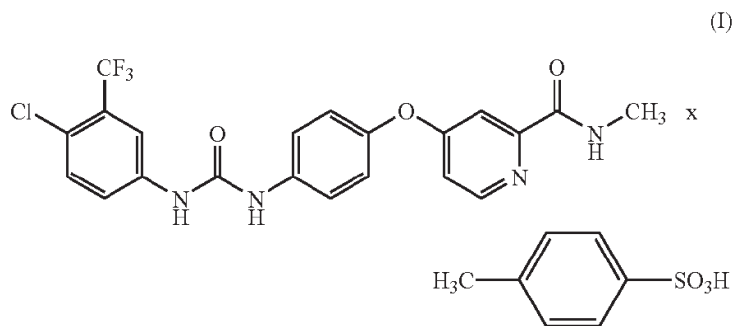
Claim 29: The compound of claim 1 which shows in the X-ray diffractometry peak maxima of the 2 theta angle comprising: 4.4, 13.2, 14.8, 16.7, 17.9, 20.1, 20.5, 20.8, 21.5, and 22.9.

C. Priority Date

79. For purposes of my analysis, I have assumed that the '933 patent is entitled to its earliest claimed priority date of September 29, 2004. My opinions would not change if it were entitled to priority only to September 20, 2005.

D. Disclosure of the Patent

80. The '933 patent relate to compound of formula (I) in the polymorph I form along with methods of preparing the compound of formula (I), where the compound of formula (I):



81. The compound of formula (I) is described in the '933 patent as “The tosylate salt of 4-{4-[(4-chloro-3-(trifluoromethyl)phenyl)amino]carbonyl)amino]phenoxy}-N-methylpyridine-2-carboxamide.” This compound is also known as sorafenib tosylate.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

82. According to the '933 patent, polymorph I is the most stable sorafenib tosylate polymorph at room temperature.²⁸

83. The '933 patent states that applicants prepared sorafenib tosylate "according to a general standard method for the preparation of tosylate salts, as described in example 1 of the working examples. In this method [sorafenib tosylate] is obtained in one crystal polymorph which is referred to below as polymorph II." '933 patent at 2:14-18.²⁹

84. The method specifically disclosed in the '933 patent for Example 1 is:

Example 1

4-{4-[(4-chloro-3-(trifluoromethyl)phenyl)amino]carbonyl]amino]phenoxy}-N-methylpyridine-2-carboxamide tosylate in the polymorph II

903 g of 4-{4-[(4-chloro-3-(trifluoromethyl)phenyl)amino]carbonyl]amino]phenoxy}-N-methyl-pyridine-2-carboxamide, prepared as described in WO 00/42012, are initially charged in 2700 ml of ethanol. 451.7 g of p-toluenesulfonic acid monohydrate are dissolved in 1340 g of ethanol and added dropwise at room temperature. The suspension is stirred at room temperature for 1 hour, then filtered off with suction, and the residue is washed three times with 830 ml each time of ethanol. The drying is effected at 50° C. under reduced pressure with supply of air. 1129.6 g of the title compound in the polymorph II are obtained.³⁰

85. The '933 patent also states that:

Surprisingly, two further polymorphs and two solvates of the compound of the formula (I) have been found. The compound of the formula (I) in the polymorph I melts under decomposition at 223-231° C., the compound of the formula (I) in the polymorph III melts at 187-190° C. The monomethanol solvate of the compound of the formula (I) contains 4.8% methanol and the monoethanol solvate of the compound of the formula (I) 6.7% ethanol. The inventive polymorph I of the compound of the formula (I) is

²⁸ '933 patent at 2:30-37.

²⁹ As explained below in section VIII, this statement is inaccurate. [REDACTED]

[REDACTED]
'933 patent at 13:35-53.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

thermodynamically stable at room temperature and is storage-stable even after processing via suspensions and is therefore particularly suitable for use in pharmaceutical formulations, for example suspensions or creams, but also in other preparations which are prepared via suspended active ingredient, for example in aqueous granulation or wet grinding.³¹

86. The '933 patent also states that:

The present invention provides the compound of the formula (I) [sorafenib tosylate] in the polymorph I. The inventive use of the compound of the formula (I) in the stable polymorph I [sorafenib tosylate] ensures that an undesired conversion to another polymorph and an associated change in the properties of the compound of the formula (I), for example solubility or bioavailability, are prevented. This increases the safety and quality of preparations comprising the compound of the formula (I) and the risk to the patient is reduced.³²

87. The patent also includes a series of additional experimental examples in which the other forms are produced. In Example 2, Polymorph II is heated to 200 °C (past the transition temperature) and then cooled to produce Polymorph I.

88. The '933 patent provides data on the properties of each of the polymorphs and solvates disclosed therein. Among other things, the patent discloses TGA and DSC analyses of each physical form. The patent also discloses PXRD patterns,³³ Raman spectroscopy and infrared spectroscopy (NIR, IR and FIR) data.

89. The DSC and TGA data presented in the '933 patent show that metastable Polymorph II and Polymorph III will convert to Polymorph I upon heating, including during the

³¹ *Id.* at 2:23-37.

³² *Id.* at 2:38-46.

³³ A calculated diffraction pattern for Polymorph I has been published. K. Ravikumar, B. Sridhar, A. K. S. Bhujanga Rao, and M. Pulla Reddy, "Sorafenib and its tosylate salt: a multikinase inhibitor for treating cancer," *Acta Crystallogr.*, C67, o29-o32 (2011). It's refcode for the CSD file is AKENUA, and that information is attached as Exhibit D.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

course of differential scanning calorimetry (DSC) experiments. Similarly, the two known solvates will desolvate and ultimately convert to Polymorph I by heating.³⁴

E. Prosecution History of the '933 Patent

90. The USPTO originally rejected claims of the '933 patent, in part, because the Examiner found that disclosure therein was inherently anticipated by the composition of N-(4-Chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-nethylcarbarnoyl)-4-pyridyloxy)phenyl) urea tosylate in the crystalline form for the treatment of cancer and tumors, which was known in the prior art.³⁵

91. In response to the Examiner's rejections, the Applicants argued that conventional methods for preparing tosylate salts would not necessarily result in the polymorph I form.³⁶

92. The USPTO rejected originally-filed claims 23, and 30-31 of the '933 patent pursuant to 35 U.S.C. § 102(b) as being inherently anticipated by Dumas (WO 03/068228) ("Dumas"). Dumas teaches a composition of N-(4-Chloro-3-(trifluoromethyl)phenyl-N'-(4-(2-(N-nethylcarbarnoyl)-4-pyridyloxy)phenyl) urea tosylate in the crystalline form for the treatment of cancer and tumors.³⁷

93. The USPTO additionally rejected originally-filed claims 24-26, and 30-37 of the '933 patent pursuant to 35 U.S.C. § 103(b) as being obvious in light of Dumas (WO 03/068228) and further in view of Sidransky (2005/0048533). The obviousness rejection was based on the Examiner's understanding that the prior art rendered it "obvious to combine two

³⁴ *Id.* at FIG. 1, 2:47-59.

³⁵ *See* May 26, 2010 Non-Final Rejection. BAYER_NEXAVAR_00087108 – 9605 at BAYER_NEXAVAR_00087558 – 568.

³⁶ *See* April 26, 2011 Pre-Appeal Request. *Id.* at BAYER_NEXAVAR_00087617 – 621.

³⁷ *See* May 26, 2010 Non-Final Rejection. *Id.* at BAYER_NEXAVAR_00087561 – 562.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition which is to be used for the same purpose.”³⁸

94. On April 26, 2011, the Applicants filed a Pre-Appeal Request for Review with the PTO, signed by Richard J. Traverso, attorney for Inventors. In addressing the Examiner’s anticipation rejection, Mr. Traverso stated:

As shown in example I of the application, conventional methods for preparing tosylate salts can result N-(4-chloro-3-(trifluoromethyl)phenyl)-N’-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea tosylate in the polymorph II form. This showing is sufficient to demonstrate the polymorph I form is not inherently produced by Dumas and this reference does not anticipate the subject matter of claims 23, 30 and 31.³⁹

95. On April 25, 2012, the PTO issued another Non-Final Rejection, again concluding that the ’933 patent is inherently anticipated by Dumas as, “the claimed tosylate appears to be the same as the prior art.”⁴⁰

96. In order to overcome the Non-Final Rejection, the Applicants filed a response, signed by Richard J. Traverso, attorney for Inventors, therein providing:

In following the teachings of Dumas, one skilled in the art would use conventional methods to form a tosylate salt and would not necessarily obtain the polymorph I form. Techniques for preparing tosylate salt forms of organic compounds are well known and the procedures are not complex. However, as Applicants have shown, three different methods have resulted in three different polymorphic forms. There is no evidence to suggest one skilled in the art would use a conventional method to prepare the tosylate salt that would inherently lead to the polymorph I form.⁴¹

97. On September 17, 2012, the PTO issued a Notice of Allowance based on:

³⁸ See *id.* at BAYER_NEXAVAR_00087562 – 564.

³⁹ See April 26, 2011 Pre-Appeal Request. *Id.* at BAYER_NEXAVAR_00087618.

⁴⁰ See April 25, 2012 Non_Final Rejection. *Id.* at BAYER_NEXAVAR_00088087.

⁴¹ July 25, 2012 Response to Office Action. *Id.* at BAYER_NEXAVAR_00088302.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Applicant's persuasive argument in which the applicants have demonstrated unexpected results and that the cited prior art does not teach p-toluenesulfonic acid which is necessary in the formation of the crystalline form of a tosylate salt of formula I.⁴²

The Applicants thereafter transmitted several Requests for Continued Examination.⁴³

98. The Examiner thereafter issued a Notice of Allowance stating that the claims were allowed because of “Applicant’s persuasive argument in which the applicants have demonstrated unexpected results and that the cited prior art does not teach p-toluenesulfonic acid which is necessary in the formation of the crystalline form of a tosylate salt of formula I.”⁴⁴

F. The Indian Opposition

99. It is my understanding that the Indian Patent Office initiated pre-grant opposition proceedings for the Indian correspondent of the '933 patent, IN 1960 DELNP/2007.⁴⁵ The parties bringing the opposition submitted, among other things, affidavits of research scientists who repeated the experiment of example 1 of the patent and analyzed the result with X-Ray diffraction.⁴⁶

100. Each research scientist repeated the procedure described for the synthesis of Sorafenib tosylate in Example 1 of the patent and each confirmed that “the repetition of these experiments yielded Sorafenib Tosylate similar to polymorph I as shown by XRPD analysis as reported in [the patent].”⁴⁷

⁴² See September 17, 2012 the PTO Notice of Allowance. *Id.* at BAYER_NEXAVAR_00088321.

⁴³ See Requests for Continued Examination. *Id.* at BAYER_NEXAVAR_00088335, BAYER_NEXAVAR_00088408, BAYER_NEXAVAR_00088919, BAYER_NEXAVAR_00088957, BAYER_NEXAVAR_00089265, BAYER_NEXAVAR_00089470.

⁴⁴ See September 17, 2012 Notice of Allowance. *Id.* at BAYER_NEXAVAR_00088316 – 322.

⁴⁵ See generally MYL_SOR00012740 – 962.

⁴⁶ *Id.* at MYL_SOR00012741 – 742.

⁴⁷ See *id.* at MYL_SOR00012942 – 962.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

G. The European Opposition

101. It is my understanding that the European Patent Office has initiated opposition proceedings involving the European correspondent of the '933 patent, EP 1797038 ("EP '038"). The parties bringing the opposition argued that they attempted to produce Polymorph II by the method of Example 1 but had invariably produced Polymorph I.⁴⁸

102. In response, Bayer apparently conducted an investigation on the method of Example 1. The results of this investigation indicated that Example 1 and Batch No. 505063 did not produce Polymorph II, but instead produced Polymorph I.⁴⁹ Bayer then conveyed their reanalysis of the retained sample of Example 1 to the EPO, indicating therein that in the reanalysis of the retained sample of Example 1, the PXRD clearly corresponded to Polymorph II.⁵⁰ Yet, the retained sample that Bayer relied on in making this conclusion was Batch No. 527319H, the micronized version of Batch No. 505158 (made by a different method than that of Example 1).⁵¹

VI. SORAFENIB TOSYLATE AND ITS CRYSTAL FORMS

103. The '933 patent states that Sorafenib tosylate is known to exist in three polymorphic forms (I, II, III), an ethanol solvate, and a methanol solvate.⁵² In addition, Bayer has identified an amorphous material,⁵³ [REDACTED]

⁴⁸ See generally Grunenberg Exh. 5 (Exhibits to the Deposition of Dr. Alfons Grunenberg ("Grunenberg Exh.")).

⁴⁹ BAYER_NEXAVAR_06775717-725 at BAYER_NEXAVAR_06775724; [REDACTED]

See MYL_SOR00012150 – 163.

⁵¹ See MYL_SOR00012166 – 167.

⁵² See '933 patent at 2:24-30.

⁵³ Grunenberg Exh. 2 at BAYER_NEXAVAR_06330024. See also BAYER_NEXAVAR_06558419-BAYER_NEXAVAR_06558456.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED] The literature reports also reports the existence of a DMSO solvate and an NMP solvate (that may be same as the isopropanol:NMP solvate) that were developed after Polymorph I and rely the disclosure of the '933 patent.⁵⁶

104. The '933 patent includes representative TGA and DSC curves for each of Polymorph I, Polymorph II and Polymorph III, the ethanol solvate and the methanol solvate.⁵⁷ It is apparent from these curves that each will melt as Polymorph I when tested by DSC or TGA.

A. The Energy Temperature System of Sorafenib Tosylate Polymorphs and Pseudopolymorphs

105. The inventors' polymorphism report [REDACTED]
[REDACTED]

⁵⁶ [REDACTED]
[REDACTED]
WO2014/118807; WO2013/175506; WO2014/138905; WO2009/092070.

⁵⁷ '933 patent at Fig. 1.

⁵⁸ Grunenberg Exh. 1 at BAYER_NEXAVAR_06329965 (Table 1).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER



106. The report also includes



 59.



HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER



107. The report confirms that [REDACTED]

[REDACTED] According to the report, [REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

[REDACTED]

108. More specifically, the report states:

- [REDACTED]
- [REDACTED]
- [REDACTED]

[REDACTED]

■ [REDACTED]

[REDACTED]

■ [REDACTED]

- [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

■ [REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

- [REDACTED]

112. [REDACTED]

[REDACTED]

B. Sorafenib Base

113. [REDACTED]

[REDACTED]

VII. BAYER'S INVESTIGATION INTO THE POLYMORPHISM OF SORAFENIB TOSYLATE

A. Bayer's Procedures

114. [REDACTED]

[REDACTED]

115. [REDACTED]

[REDACTED]

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

118. Dr. Grunenberg testified that the [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

119. I also understand that Plaintiffs [REDACTED]

[REDACTED]

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[illegible]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

129.

C.

134. More specifically, the polymorphism screening report indicates:

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[illegible]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

115

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER



HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER



In this table, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

VIII. THE METHOD OF EXAMPLE 1 PRODUCES POLYMORPH I, NOT II

167. I understand that Plaintiffs contend that the method of Example 1 of the '993 patent corresponds to Batch 505063, and that this method and this batch produced Polymorph II. This is what is stated in the '933 patent, and it is what Plaintiffs have told various patent offices throughout the world.

168. I disagree. Although the method of Example 1 corresponds to Batch 505063, this batch this method did not produce Polymorph II. It produced Polymorph I.

A. Batch 505063 Corresponds to Example 1 of the '933 Patent

169. The method used to make Batch 505063 corresponds to Example 1 of the '933 patent. I have reviewed the disclosure of the batch record and the disclosure of the patent. This is consistent with Dr. Grunenberg's statements in his declaration [REDACTED]. His declaration states that "[i]n July 1999, I obtained a first sample of sorafenib tosylate (505063) together with its manufacturing protocol (Enclosure 2) which is identical to the

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

manufacturing protocol described in Example 1 of the patent.”¹³¹ [REDACTED]

[REDACTED]

170. For example, during the European opposition proceeding, Dr. Grunenberg submitted a declaration stating his opinion that this batch was in Polymorph II based on a DSC taken on July 23, 1999. He acknowledged that the endotherm that he identified as Polymorph II did not match the known data for Polymorph II, but he wrote that:

The slight shift in the onset temperatures can be explained by common kinetic effects and also depends on the particle size and purity of the sample. The presence of the minor endothermal peak is clear evidence that the samples are not in the modification of polymorph I but in the modification of polymorph II.¹³³

171. When asked in deposition, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

172. Dr. Grunenberg’s declaration also omitted the existence of other analytical data for this batch, including the Raman and IR spectroscopy data.

173. Dr. Grunenberg’s declaration says that Batch 505063 was not analyzed by PXRD. But this is not true. [REDACTED]

[REDACTED]

¹³¹ Grunenberg Exh. 3 at MYL_SOR00012607.

¹³³ *Id.* at MYL_SOR00012608 (emphasis added).

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

[REDACTED]

174. [REDACTED]

175. In my opinion, the available data for Batch 505063 are most consistent with Batch 505063 being prepared as Polymorph I together with an impurity that is likely sorafenib base,

[REDACTED]

176. [REDACTED]

[REDACTED] does not establish the presence of Polymorph II. [REDACTED]

[REDACTED]

[REDACTED] Further, the data are not consistent with the conversion of Polymorph II to Polymorph I over time because [REDACTED]

[REDACTED]

[REDACTED]

1. [REDACTED]

177. [REDACTED]





































[REDACTED]

[REDACTED]

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

178. I have reviewed the procedures used to prepare each of Batch Nos. 505003, 505004 and 505063. [REDACTED]

2. _____

141

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

183. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

3. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

142 [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]					
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]					
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

155

was that of Polymorph I, as shown in Exhibit C To generate accurate frequencies for the peaks in the spectrum, I ran optical character recognition on the pdf document to orient the spectrum horizontally before importing the file into Adobe Photoshop as a raster scan with 800 dpi resolution. After checking the orientations of the plot (which needed no further adjustment), I smoothed pattern manually to eliminate rastering artifacts in which the plot doubled back on itself. This process had no material affect on the frequencies obtained. This procedure allowed me to use Un-Scan-It Gel (version 6.1, Silk Scientific, Inc.) to digitize the pattern using the bottom part of the trace for the digitization. Peak positions were assigned visually with CrystalDiffract 6.6.0 from CrystalMaker Software, Ltd.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

191. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

192. [REDACTED]

[REDACTED]

[REDACTED]

159 [REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER



HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

[REDACTED]

4. Other Polymorph I Batches [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

5. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(i) Bayer's Experiments [REDACTED]

161 [REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

197. Plaintiffs conducted experiments [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

199. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

202. [REDACTED]

[REDACTED]

166

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Government	Percentage
Current government	85%
Previous government	15%

[illegible]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

206.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

B. Polymorph II [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

208. I have reviewed [REDACTED] [REDACTED] [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(i) All reported attempts [REDACTED]

210. There are have been many attempts [REDACTED]

[REDACTED]

181

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

(a) [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

(ii) Batch 505063 is Inconsistent with a “Disappearing Polymorph”

213. Dr. Grunenberg and Bayer have argued that others’ failure to obtain Polymorph II is explainable because Polymorph II is a “disappearing polymorph.” Under this theory, once Polymorph I was made it became impossible to make Polymorph II because of seeding from Polymorph I.¹⁸⁷

214. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

184

[REDACTED]

187 See e.g., MYL SOR00012567 – 592 (Affidavit of Dr. Roland Boese and Exhibits);

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

215. Polymorph II as a disappearing polymorph is more plausible if, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

C. All Reported Attempts to Reproduce Example I have Produced Polymorph I.

1. The Indian Opposition

217. During the Indian pre-grant opposition proceedings, the opponents attempted to reproduce method of Example 1 in the '933 patent. They reported that that their attempts produced Polymorph I.¹⁸⁸ As indicated therein, “[t]he opponent being engaged in the research and development as well as the manufacture of drugs/medicinal compositions repeated the experiment given in working example 1 of the impugned application for the preparation of the tosylate salt of Sorafenib. However, contrary to the applicant’s statement polymorph-I was obtained by following the procedure given in example I of the impugned application.”¹⁸⁹ They also reported that attempting to make sorafenib tosylate by following an alternative method known in the art also resulted in Polymorph I.¹⁹⁰

¹⁸⁸ See MYL_SOR00012740 – 962 at MYL_SOR00012751.

¹⁸⁹ *Id.*; see also MYL_SOR00013757 – 815 at MYL_SOR00013759, MYL_SOR00013767, MYL_SOR00013784.

¹⁹⁰ See MYL_SOR00012740 – 962 at MYL_SOR00012752.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

218. Each research scientist repeated the procedure described for the synthesis of sorafenib tosylate in Example 1 of the patent, and each confirmed that “the repetition of these experiments yielded Sorafenib Tosylate similar to polymorph I as shown by XRPD analysis as reported in [the patent.]”¹⁹¹ I have reviewed the PXRD patterns of the resulting samples and agree that they are Polymorph I.

2. The European Opposition

219. During the European opposition proceedings, opponents attempted to reproduce method of Example 1 in the ’933 patent. They reported that their attempt to produce Polymorph I failed.¹⁹² As indicated in the summary of proceedings, “[t]he two Opponents have repeated the synthetic procedure of example 1 in their respective laboratories and both came to the result that they could not obtain polymorph II contrary to the procedure disclosed in the description of the patent.”¹⁹³ . Instead, “[t]he two Opponents independently obtained polymorph I directly when repeating example 1 of the patent in suit. They have further argued that there are doubts that the Patentee had indeed obtained polymorph II when carrying out example 1.”¹⁹⁴

220. I have reviewed the experimental results reported in accompanying declarations.¹⁹⁵ The material produced was Polymorph I.

3.

¹⁹¹ See *id.* at MYL_SOR00012942 – 962.

¹⁹² Grunenberg Exh. 5 at p. 6.

¹⁹³ *Id.* at 11.

¹⁹⁴ *Id.*

¹⁹⁵ MYL_SOR00011570 – 590 (Fresenius); MYL_SOR00011751 – 767 (Biofer Sp.A.).

¹⁹⁶

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

4. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

IX. LEGAL BACKGROUND

A. Level of Ordinary Skill in the Art

225. I understand that whether a patent claim is invalid is determined from the perspective of a person of ordinary skill in the art.

226. I also understand that defining a person of ordinary skill in the art is based on several factors: (1) the educational level of the inventors; (2) the type of problems encountered in

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

the art; (3) the prior art solutions to those problems; (4) the rapidity with which innovations are made; (5) the sophistication of the technology; and (6) and the educational level of workers in the field.

227. The patents-in-suit encompass, among other things, aspects of pharmaceuticals related to organic chemistry, analytical characterization of synthesized compounds, X-ray crystallography, and drug formulation. I understand that the named inventors of the asserted patents generally had advanced degrees in the field of chemistry and experience in the field. Dr. Alfons Grunenberg has a Ph.D. in Chemistry and had worked at Bayer for about 25 years, primarily working on crystal modifications and polymorphism of organic compounds and thermal analysis.²⁰¹ Dr. Jana Lenz has a Ph.D. in Pharmacy and has been working for Bayer since 2000, primarily in chemical development dealing with the development of active pharmaceutical ingredients.²⁰²

228. In my opinion, with respect to the '933 patent, the person of ordinary skill in the art ("POSA") would have had, at the time of the claimed invention, a Ph.D. in Chemistry, chemical engineering, pharmaceuticals, pharmaceutical sciences, or a related discipline. Alternatively, the POSA may have had a lesser degree in one of those fields, such as a Master's degree, with correspondingly more experience. The POSA would have experience in identifying compounds using data derived from analytical techniques (*e.g.*, PXRD, single crystal X-ray diffraction, infrared and Raman spectroscopy, and differential calorimetry). In addition, such a person would have consulted with others with necessary expertise in the pharmaceutical industry, such as a formulator or medical doctor.

²⁰¹ Grunenberg Exh. 3.

²⁰² Lenz Tr. 9:1-11:20.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

229. I have been asked by counsel for Defendant to provide my expert opinion on the validity of the asserted claims, from the perspective of a POSA. My opinions as they relate to invalidity are the same under either the Defendant's or Plaintiffs' definition of a POSA.

B. Priority Date and Prior Art

230. I understand prior art is what is known in the art prior to the priority date of a patent. A patent is entitled to a priority date at least as early as the date it was filed. I also understand that patent may be entitled to the benefit of the filing date of an earlier application as long as certain legal criteria are met.

C. Anticipation

231. I understand that for a claim to be anticipated, it is necessary that a single prior art reference disclose each limitation of the claim, either expressly or inherently. I also understand that a claim limitation not expressly found in a reference may nonetheless be inherent if the art described in the reference necessarily functions in accordance with, or includes, the claimed limitations.

232. Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates.

233. I also understand that the discovery of a previously unappreciated property of a prior art composition, or of a scientific explanation for the prior art's functioning, does not render the old composition patentably new to the discoverer.

234. Inherency is not necessarily co-extensive with the knowledge of those of ordinary skill in the art. That is, inherent anticipation does not require an appreciation of the inherent limitation by those of skill in the art before the critical date of the patents at issue.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

D. Obviousness

235. I understand that a claim may be obvious if it is a predictable improvement or combination of prior art elements according to their established functions.

236. I also understand that I may consider the interrelated teachings of multiple references and the background knowledge possessed by a POSA at the time of the invention, to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patents at issue.

237. I understand that I may take into account the inferences and ordinary creativity that a POSA would employ.

238. I have been asked to determine if certain claims of the asserted patents would have been obvious in 2004 to a POSA, in light of the prior art.

239. In analyzing the question of obviousness, I have been asked to consider: (i) the scope and content of the prior art, (ii) the differences between the prior art and the claims at issue, (iii) the level of ordinary skill in the art, and (iv) secondary considerations, if any, of nonobviousness.

240. I understand that a patent claim can be invalid as obvious if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to a POSA at the time of the invention. Further, I understand that in an obviousness analysis, it is important to show that a POSA would have a motivation to combine the teachings of the prior art references to arrive at the claimed invention, and that a POSA would have a reasonable expectation of success in arriving at the claimed subject matter. I also understand that an inherent characteristic of an otherwise obvious combination does not render the subject matter patentable. I further understand that Plaintiffs may rely on evidence of

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

secondary considerations of non-obviousness, and that I will be allowed an opportunity to rebut any identified alleged secondary considerations.

E. Obviousness-Type Double Patenting

241. I have been informed that only one patent may be obtained for a single invention. I have also been informed that this requirement – referred to as the ban against “double-patenting” – prohibits a person from securing more than one patent for either (a) the same invention or (b) an obvious modification of the same invention (or, “obviousness-type double patenting”). Principles of anticipation also can apply in an obviousness-type double patenting analysis.

242. I have been informed that, under the doctrine of obviousness-type double patenting, a claim may be rendered invalid by an earlier claim even if that earlier claim is not prior art. Specifically, an earlier claim that shares a common inventor, assignee, or owner with a later claim can render obvious that later claim.

243. I further understand that the analysis proceeds in a manner similar to anticipation or obviousness, depending on the particular facts of the case with certain differences. The prior claim is not treated as prior art. Instead the determination is whether the later claim is an obvious variant of the earlier claims. In addition, a POSA need not have reasons to select the earlier claim as a starting place. I further understand that whether secondary considerations may not be used in an obviousness-type double patenting is unsettled.

F. Inventorship

244. I understand that inventorship has two parts: (1) conception and (2) reduction to practice. Conception is the touchstone of inventorship, which is the completion of the mental part of invention. I understand that conception is

the formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice. An idea is sufficiently definite

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

and permanent when only ordinary skill would be necessary to reduce the invention to practice, without extensive research or experimentation.

245. Reduction to practice may be actual or constructive. Actual reduction to practice occurs when an embodiment of the claimed invention is made and it has some use. Filing a patent application that enables the practice of the invention is deemed conception and constructive reduction to practice.

246. Inventorship may be sole or joint. Each joint inventor must generally contribute to the conception of the invention and a contribution to one claim is enough. In order to be joint inventor, a person's contribution to the claimed invention must not be insignificant in quality and must do more than explain well-known concepts or the current state of the art. The mere identification of inherent properties of a compound is not an inventive act.

247. Derivation is a related concept. I understand that to prove derivation under § 102(f), the party asserting invalidity must prove both [1] prior conception of the invention by another and [2] communication of that conception to the patentee. The communication must be sufficient to enable one of ordinary skill in the art to make the claimed invention.

G. Legal Presumption

248. I have been informed that an issued patent is presumed valid, and that invalidity of a claim must be demonstrated by defendants through clear and convincing evidence.

X. PRIOR ART AND DOUBLE PATENTING REFERENCES

A. WO 03/068228 (“WO 228” or “Dumas”)

249. Sorafenib tosylate is admitted prior art to the '933 patent. The '933 patent states “sorafenib tosylate is disclosed in the prior art in WO 03/068228” (“WO 228”) which was published more than one year before the priority date of the '933 patent and is therefore prior art under at least 35 U.S.C. § 102(b).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

250. WO 228 states: “The present invention provides a method for treating diseases in humans or other mammals which are mediated by the VEGF induced signal transduction pathway, including those characterized by abnormal angiogenesis or hyperpermiability processes. These methods comprise administering a compound of formula I below or a salt, prodrug or stereoisomer thereof to a human or other mammal with a disease characterized by abnormal angiogenesis or hyperpermiability processes.”²⁰³

251. Claim 22 of WO 228 specifically discloses sorafenib tosylate and a method of using it: “A method of treating diseases mediated by the VEGF-induced signal transduction pathway comprising administering the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N’-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea tosylate.” The body of WO 228 discloses sorafenib tosylate free base and a method of making it as Example B. It also discloses 4-toluene sulfonic acid as a potential salt-forming acid, which is also known as para- or p-toluenesulfonic acid.²⁰⁴

B. U.S. Patent No. 7,351,834 (“the ’834 patent”)

252. U.S. Patent No. 7,351,834 (“the ’834 patent”) claims priority to an application filed January 13, 1999. It issued April 1, 2008. It expires January 12, 2020, according to the Orange Book. The ’834 patent is prior art to the ’933 patent.

253. The compounds are described as useful as drug for the treatment of human diseases. The compounds of the patent (including sorafenib) are described as “useful in pharmaceutical compositions for human or veterinary use” including the treatment of “human or

²⁰³ WO 228 at 4:4-8.

²⁰⁴ WO 228 at 75:1-4.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

animal solid cancers” and useful in a “method for treating raf mediated disease state in humans or mammals.”²⁰⁵

254. Claim 41 is directed to: “A compound of claim 39 which is a tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N’-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea.”

255. N-(4-chloro-3-(trifluoromethyl)phenyl)-N’-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea is a chemical name for sorafenib tosylate.

C. U.S. Patent No. 8,618,141 (“the ’141 patent”)

256. U.S. Patent No. 8,618,141 (“the ’141 patent”) claims priority to an application filed February 11, 2002. It issued December 31, 2013. It expires February 11, 2023 according to the Orange Book.

257. Claim 6 is directed to:

6. A method of blocking tumor angiogenesis in a human or other mammal comprising administering to a human or other mammal with a tumor of the breast, gastrointestinal tract, kidney, ovary or cervix, an effective amount of the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea tosylate.

258. Claim 10 depends from Claim 6:

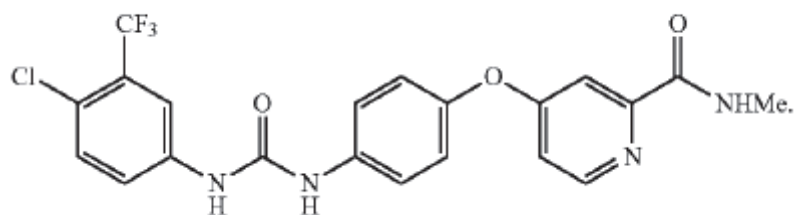
10. The method of claim 6, wherein the effective amount of the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N’-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea tosylate is between 0.01 to 200 mg/Kg of total body weight.

259. Claims 7-9 and 11 are directed to:

7. A method of blocking angiogenesis in a tumor of the kidney comprising administering to a human or other mammal with a tumor of the kidney an effective amount of the tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N’-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula below

²⁰⁵ ’834 patent at 1:55-2:14.

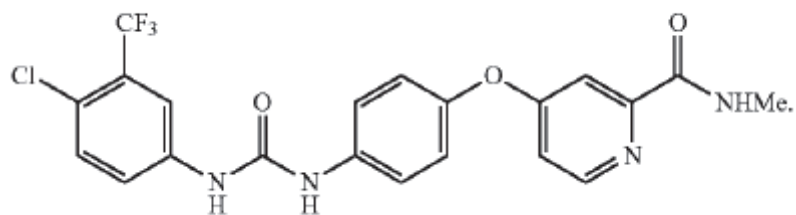
HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER



8. A method as in claim 7 wherein the tumor of the kidney that is treated is characterized by abnormal angiogenesis or hyperpermiability processes, which are not raf-mediated nor p38-mediated.

9. A method as in claim 8 wherein the tumor of the kidney that is treated is characterized by abnormal angiogenesis or hyperpermiability processes, which are mediated by KDR (VEGFR-2).

11. The method of claim 7, wherein the effective amount of the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula below is between 0.01 to 200 mg/Kg of total body weight



D. Art Related to the Preparation of Salts

260. Tosylate salts are formed by combining a base with p-toluenesulfonic acid.

Sorafenib tosylate is the salt formed by combining sorafenib base and p-toluenesulfonic acid (PTSA).

261. The formation of an acid-addition salt such as sorafenib tosylate is a simple well-known process that has been known and practiced for more than a century.

262. Tosylate salts and methods preparing them were known in the prior art. *See, e.g.*, Stahl (2002) at 309-10; U.S. Patent No. 5,659,030 (crystalline cephalosporin tosylate salt); Numerous prior art reference disclose tosylate salts and methods of making them, such as U.S.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Patent No. 3,065,136 (itrimin tosylate); U.S. Patent. No. 4,831,025 (sultamicillin tosylate); U.S. Patent No. 6,093,814 (cefdinir tosylate); WO 2004/072085A2 (clopidogrel tosylate); U.S. Patent No. 6,608,206 (S(-)Amlodipine tosylate); U.S. Patent No. 7,094,930 (sertraline tosylate); WO 2002/030900A (Non-deliquescent salt of 4-hydroxypiperidine derivative). *See also* Piotr Milart & Katarzyna Stadnicka, “Salts of 4-(2,4,6-Triphenyl-1-pyridinio)phenolate with *p*-Toluenesulfonic Acid in Molar Ratio 1:1 and 2:1 – Crystal and Molecular Structure,” *Eur. J. Org. Chem*, 2001(12), 2337-2441 (2001); C. R. Noller & Poe Liang, “Para-Toluene Sulfonates as Derivatives for the Identification of Aromatic Amines,” *J. Soc. Chem. Ind.*, 54, 670-673 (Feb. 1932); H. K. Hall, Jr., “Steric Effects on the Base Strengths of Cyclic Amines,” *J. Am. Chem. Soc.*, 79, 5444-5447 (1957).

263. Plaintiffs’ apparently agree. During prosecution of the ’933 patent, Plaintiffs said to the USPTO that “[t]echniques for preparing tosylate salt forms of organic compounds are well known and the procedures are not complex.”²⁰⁶

E. Sorafenib

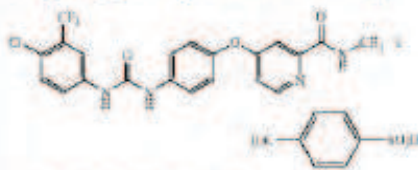
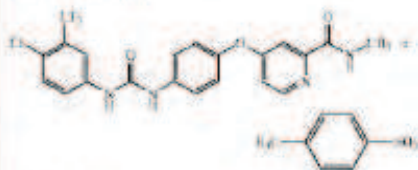
264. As of the priority date, sorafenib tosylate was a drug undergoing clinical development and Plaintiffs were seeking approval to market it as a drug for human use in the United States and other countries. For example, “BAY 43-9006: Preclinical Data”²⁰⁷, cited during the prosecution of the ’933 patent states that sorafenib (as Bay 43-9006) was currently undergoing clinical trials.

²⁰⁶ July 25, 2012, Response to Office Action of April 25, 2012.
BAYER_NEXAVAR_00087108 – 9605 at BAYER_NEXAVAR_00088302.

²⁰⁷ *See* August 26, 2010 Reply to Office Action mailed 05/26/2010.
BAYER_NEXAVAR_00087108 – 9605 at BAYER_NEXAVAR_00087580 (citing Wilhelm et al., “BAY 43-9006: Preclinical Data,” *Curr. Pharm. Des.*, 2002, Vol. 8, Number 25, pp. 2255-2257, Exhibit B (BAYER_NEXAVAR_00087588 – 590)).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER**XI. CLAIM CONSTRUCTION**

265. I understand that the parties have stipulated to the meaning of certain terms in the '933 patent.²⁰⁸

Claim	Term	Parties' Agreed Upon Construction
'933 patent: 1, 2, 8,16, 27-30	peak maxima of the 2 theta angle [peak information]	peak maxima of the 2 theta angle [peak information] \pm 0.2
'933 patent: 8	<p>A pharmaceutical composition comprising a compound of formula (I)</p>  <p>substantially in the polymorph I form</p>	<p>A pharmaceutical composition comprising a compound of formula (I)</p>  <p>wherein the compound of formula (I) in the composition is largely, but not necessarily wholly, in the polymorph I form</p>

266. The remaining terms are to be given their plain and ordinary meaning.

XII. INVALIDITY OVER THE PRIOR ART AND INVALIDITY DUE TO DOUBLE PATENTING**A. Polymorph I is Inherently Anticipated (or Obvious Over) Conventional, Prior Art Methods of Making Tosylate Salts**

267. Polymorph I of sorafenib tosylate is the inherent result of conventional methods of making sorafenib tosylate: methods known or obvious to a POSA as of the time of the invention would have produced Polymorph I as disclosed in, e.g., WO 228. Example 1 of the '933 patent is one such method, and, as described above, this method produces Polymorph I (contrary to the '933 patent's assertion that it produces Polymorph II). As a result, Claims 1-2 and 27-28 are anticipated or obvious, or are invalid due to obviousness-type double patenting.

²⁰⁸ Oct. 14, 2016 Joint Claim Construction Chart, Dkt. No. 92-1 at 3-4.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

268. As explained above, the prior art discloses sorafenib and a method of making it, in, *e.g.*, Dumas. (See above, Section X). The prior art also discloses tosylate salts and methods of making them through the use of p-toluenesulfonic acid. Thus, as of the priority date of the '933 patent, a POSA would have known how to prepare the tosylate salt of sorafenib.

269. In order to practice sorafenib tosylate as disclosed in, *e.g.*, Dumas, or as claimed in the '141 patent, a POSA would have to make sorafenib tosylate. To do so, a POSA would have used sorafenib base together with PTSA through a conventional method of making tosylate salts. This does not appear to be in dispute. Bayer argued to the USPTO during prosecution that, “[i]n following the teachings of Dumas, one skilled in the art would use conventional methods to form a tosylate salt”²⁰⁹

270. The process of Example 1 is one such “conventional method.” It is described in the '933 patent as the application of a “general standard method” for making tosylate salts.²¹⁰ During the prosecution of the '933 patent, the Applicants argued:

As shown in example I of the application, conventional methods for preparing tosylate salts can result [in sorafenib tosylate] in the polymorph II form. This showing is sufficient to demonstrate the polymorph I form is not inherently produced by Dumas and this reference does not anticipate the subject matter of claims 23, 30 and 31.²¹¹

271. Similarly, during the prosecution of the European counterpart of the '933 patent, Bayer wrote:

Usually the preparation of a salt of a known compound follows a standard procedure which is *e.g.* solving the base and the acid in a solvent and let the resulting salt crystalizing as described in *e.g.*

²⁰⁹ See July 25, 2012 Response to Office Action. BAYER_NEXAVAR_00087108 – 9605 at BAYER_NEXAVAR_00088302.

²¹⁰ '933 patent at 2:13-16

²¹¹ April 26, 2011 Pre-Appeal Request. BAYER_NEXAVAR_00087108 – 9605 at BAYER_NEXAVAR_00087618 (emphasis added).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

in example 1 of the present application. **According to such a protocol the tosylate salt mentioned in [Dumas] can be prepared and that was initially done in our laboratories.** The result was that [sorafenib tosylate] was obtained in the metastable polymorph II. That means the standard procedure yields [sorafenib tosylate] in the metastable polymorph II.²¹²

272. [REDACTED]

1. The Metastable Polymorphs and the Solvates Are Not Made by Conventional, Prior Art Methods

273. Attempts by a POSA to make sorafenib tosylate by any of the typical methods for making tosylate salts as of the priority date would have resulted in Polymorph I. In other words, a POSA looking simply to make sorafenib tosylate as disclosed in e.g., WO 228 (and not to investigate its polymorphism) would have used methods that produced Polymorph I. Although the other polymorphs and pseudopolymorphs appear to have been prepared by conventional techniques for investigating polymorphism, none of them were made by the kinds of methods a POSA would have chosen simply to synthesize the material in the first instance. Polymorph II was not made by conventional method and was not reproducible as of the priority date.

274. The critical factors for the preparation of Polymorph II are unclear because neither [REDACTED]

[REDACTED] No one knows. [REDACTED]

(i) Polymorph III was not the product of conventional methods

²¹² MYL_SOR00011392 – 393 at MYL_SOR00011393 (emphasis added).

²¹³ [REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

275. Polymorph III also was not produced by a conventional method like that of Example 1. Polymorph III is prepared from Polymorph II (or Polymorph I). According to the '933 patent,

Polymorph III can be prepared by effecting the compound of the formula (I) in the polymorph II in an inert solvent, for example methanol. Filtration is effected after from 1 day to 1 week, and the product is dried and heat-treated at from 145 to 160° C. for from 15 minutes to 1 hour. The compound of the formula (I) is thus obtained in the polymorph III.²¹⁴

276. Although this a conventional method of searching for polymorphs, it is not a conventional method of simply attempting to prepare a tosylate salt. A POSA would not “effect” the compound in solvent for one day to one week when trying to prepare sorafenib tosylate in the first instance since, as written, this procedure requires crystalline sorafenib tosylate as a starting material.

277. The ethanol and methanol solvates were also not produced by conventional methods like that of Example 1. Again, each of these methods started with a crystalline form of sorafenib tosylate.

278. According to the '933 patent the methanol solvate is prepared by effecting the compound of the formula (I) in the polymorph II in methanol. After 1 week, filtration is effected, and the product is dried and stored under a methanol atmosphere for from 5 hours to 1 week. The methanol solvate of the compound of the formula (I) is thus obtained with a methanol content of 4.8% by weight.

'933 patent at 13:3-9.

279. According to the '933 patent the ethanol solvate is prepared by effecting the compound of the formula (I) in the polymorph II in ethanol. After 1 week, filtration is effected and the

²¹⁴ '933 patent at 12:63-13:2.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

product is dried. The ethanol solvate of the compound of the formula (I) is thus obtained with an ethanol factor of 6.7 percent by weight.

'933 patent at 13:10-15.

280. A POSA would not prepare a salt for the first time by effecting it in solvent for one week since, again, this procedure, as written, requires crystalline sorafenib tosylate as a starting material.

281. The literature also reports other methods of making the solvates and Polymorph III, but these patent applications were prepared following (and directly referencing) the disclosure the '933 patent. In my opinion, these procedures were not ones that a POSA would have chosen for the initial synthesis of sorafenib tosylate for the purpose of practicing, *e.g.*, WO 228.²¹⁵

282. As a result, Polymorph I is anticipated or obvious. For similar reasons, Claims 1-2 and 28-29 are invalid for obviousness-type double patenting over *e.g.*, Claim 6-11 of the '141 patent. Sorafenib tosylate is either "anticipated" by that claim or is otherwise an obvious variant of them.

B. Polymorph I is Inherently Anticipated (or Obvious) by Standard Analytical Techniques

283. Even if Polymorph I were not initially obtained from the initial synthesis of sorafenib tosylate, it would be the inevitable result of heating any other of the known crystalline form or the amorphous form of sorafenib tosylate disclosed in the '933 patent. [REDACTED]

[REDACTED]

[REDACTED]

²¹⁵ WO2014/118807; WO2013/175506; WO2014/138905; WO2009/092070.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED] Routine analytical procedures that a POSA would have conducted, such as taking a melting point, or conducting a DSC or TGA would have inherently produced Polymorph I.

284. A POSA would have used standard techniques to obtain a melting point when analyzing any form of sorafenib tosylate produce from synthesis. Taking a melting point is almost invariably one of the first steps in characterizing a newly synthesized compound.

285. For example, Giron (2004) states:

The melting point of organic substances is one of the first properties measured. A number of techniques are available, from immediate melting to the capillary method described in various pharmacopoeias. The substance is heated and the transition to the liquid phase is observed visually or by hot-stage microscopy. Generally the melting point is measured by DSC. Some polymorphs may have differences of melting points less than 1°C or differences more than 100°C.²¹⁷

286. This is particularly true for salts, as Giron (2002) explains:

The melting point of a new organic substance is one of the first properties measured. A number of techniques are available, from immediate melting to the capillary method described in various pharmacopoeias, in which the substance is heated and the transition to the liquid phase is observed visually or by hot-stage microscopy. [DSC] allows the change of enthalpy during melting to be followed and the thermal processes to be determined quantitatively. **Because processing and milling involve the evolution of heat, the melting point is an important property in the choice of the salt candidate.**²¹⁸

287. [REDACTED]

²¹⁶ [REDACTED]

²¹⁷ Giron, D., *et al.*, "Solid-State Pharmaceutical Compounds, Impact of the ICH Q6 guidance on industrial development," *Journal of Thermal Analysis and Calorimetry*, 77, 709-747 (2004) at 727 (emphasis added) ("Giron (2004)").

²¹⁸ Giron (2002) at 50 (emphasis added).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

[REDACTED]

[REDACTED]

288. As described above, every known crystalline form of sorafenib tosylate will convert to Polymorph I in the course of conventional analytical techniques. For example, taking the DSC of Polymorph II (to the extent it could be obtained), Polymorph III or the solvates would have inevitably resulted in Polymorph I. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

289. Thus, to the extent a POSA's attempts to prepare sorafenib tosylate did not initially produce Polymorph I, the use of any of these and other standard analytical techniques would have inevitably produced Polymorph I.

290. As a result, Polymorph I is anticipated or obvious. For similar reasons, Claims 1-2 and 28-29 are invalid for obviousness-type double patenting over e.g. Claim 6-11 of the '141 patent. Sorafenib tosylate is either "anticipated" by that claim or is otherwise an obvious variant of them.

C. Polymorph I is Obvious Because it is the Most Stable Form at Room Temperature

291. Each of the claims 1-2 and 28-29 of the '933 patent is invalid as obvious over the prior art for the reasons described above and in this section, and are invalid for obviousness-type double patenting. I incorporate my analysis of anticipation above into this section. To the extent

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

that these claims are not rendered anticipated or obvious as described above, they are nevertheless obvious.

292. In addition, Polymorph I would have been the obvious result of a conventional search for the most stable polymorph as explained below.

1. Scope and Content of the Prior Art for Obviousness and Scope of the Earlier-expiring claims

293. The scope and content of the prior art, as well as the differences between the claims and the prior art, are described above and below. Generally, sorafenib tosylate was known, sorafenib base and a method of making it were known, and methods of making tosylate salts were known. The scope and content of the prior art, as well as differences between the claims and prior art, is further described below. The only real difference between the prior art and the claim is that polymorphic form is not explicitly disclosed in the prior art.

2. Motivation to Identify the Most Stable Form and Expectation of Success in Obtaining the Most Stable Polymorph

294. A POSA would have been strongly motivated to investigate crystal forms of sorafenib tosylate and, in particular, to identify the most stable form. The prior art identified sorafenib as entering clinical trials, and specifically disclosed and claimed sorafenib tosylate as useful for human use.²²² Because sorafenib tosylate was intended for human use, it was subject to guidance mandating an investigation into polymorphic forms.²²³ As the ICH Q6A Guidelines note, polymorphism and pseudopolymorphism must be investigated because “[d]ifferences in

²²² See above, e.g., ¶ 264.& § X.A-C.

²²³ See, e.g., “Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances,” Food and Drug Administration (February 1987) (“FDA Guideline 1987”); “Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Products: Chemical Substance Q6A,” Step 4, ICH (October 1999) (ICH Q6A Guidelines). The ICH Q6A 1999 guidelines were adopted by the FDA in 2000 in Federal Register Vol. 65, No. 251, pp. 83041-83063. (“FDA Guidance on Q6A Specification (2000)”)

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

these forms could, in some cases, affect the quality or performance of the new drug products.”²²⁴ In fact, the very first step of the relevant decision tree of ICH Q6A 1999 guidance is “Conduct polymorphism screen on drug substance”:²²⁵

(i) A POSA Would Have Had an Expectation that Sorafenib Tosylate Would Be Likely to Exhibit Polymorphism

295. A POSA would have had a reasonable expectation that sorafenib tosylate would be likely to exhibit polymorphism or pseudopolymorphism and would have had a reasonable expectation of success in identifying the most stable polymorph.

296. A very large fraction of pharmaceutical compounds demonstrate polymorphism.²²⁶ As one of the inventors, Dr. Grunenberg has written, “Polymorphism occurs frequently in organic compounds. It has been shown that about 80% of drug substances are polymorphic.”²²⁷

297. Walter McCrone states, “It is at least this author’s opinion that every compound has different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound.” W. C. McCrone, “Polymorphism” Chapter 8 in *Physics and Chemistry of the Organic Solid State*, Interscience Publishers, New York, NY (1965) at 727.

²²⁴ ICH Q6A Guidelines at 8.

²²⁵ ICH Q6A Guidelines at 24.

²²⁶ See Haleblan (1969) at 912 (“The scientific literature also included numerous indications of [polymorphism’s] importance in pharmaceuticals. . . . It is now apparent that most, if not all, compounds and elements show a variety of different crystal forms.”).

²²⁷ A. Grunenberg, *et al.*, “Theoretical derivation and practical application of energy/temperature diagrams as an instrument of preformulation studies of polymorphic drug substance,” *International Journal of Pharmaceutics*, 129, 147-158 (1996) (“Grunenberg (1996)”) (citing A. Grunenberg, “Thermische Methoden, Thermoanalyse,” In *Apothekammer Nordrhein (Ed.), Regelweiterbildungsseminar Pharmazeutische Analytik*, Bonn, (1992)).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

298. Numerous authors have either cited this statement by McCrone or have quoted him directly. In his 1987 chapter on conformational polymorphism Bernstein quotes McCrone directly, prefacing the quote by stating:

Because of its industrial importance, examples of polymorphism and techniques for investigating and utilizing it come from those areas of chemical research where full characterization of a material is crucial in determining its ultimate use, *e.g.* in pharmaceutical, dyes, and explosives. Various aspects of the subject have been treated in books and a number of reviews. The ubiquity of the phenomenon is still not generally recognized, although over twenty years ago McCrone suggested that virtually “every compound has different [sic] polymorphic forms...the number of forms for a given compound is proportional to the time and energy spent in research on that compound.”

See J. A. Bernstein, “Conformational Polymorphism,” in *Organic Solid State Chemistry*, G. R. Desiraju, ed., Elsevier, Amsterdam, 471-518 (1987) at 472 (“Bernstein (1987)”).

299. Bernstein quotes this same passage in the introduction to his 2002 book entitled “Polymorphism in Molecular Crystals” (J. A. Bernstein, Oxford University Press, Oxford (2002), at 9). Clearly, already by 1987, Bernstein recognized the industrial importance and “ubiquity” of polymorphism. By 2002, when his book on polymorphism was published, the importance and ubiquity of polymorphism were even more established and widely recognized in the field of pharmaceutical chemistry. He wrote: “The increasing awareness and importance of polymorphism in the past 30 years or so is perhaps nowhere more evident than in the field of pharmaceuticals. ... The literature on the polymorphism of pharmaceuticals is now best described as vast.”²²⁸

²²⁸ (Bernstein (2002) at 240.)

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

300. Bernstein's sentiments are echoed by numerous authors, including Guillory and Caira. Guillory, while citing the 1965 McCrone article, quotes an equivalent statement from a 1957 publication by McCrone: "Those who study polymorphism are rapidly reaching the conclusion that all compounds, organic and inorganic, can crystallize in different forms or polymorphs. In fact, the more diligently any system is studied, the larger the number of polymorphs discovered." Guillory (1999) at 185. Guillory prefaces this quote with a provocative question:

One question that is likely to arise during the registration process is "What assurance can be provided that no other crystalline forms of this compound exist?" It is incumbent on the manufacturer of a new drug substance to show that due diligence has been employed to isolate and characterize the various solid-state forms of a new chemical entity. This may seem to be a daunting task, particularly in light of the widely quoted statement by Walter C. McCrone [2] that ...

Guillory (1999) at 185.

301. Caira 1988²²⁹ paraphrases McCrone in a way that makes it clear that the *absence* of polymorphism is unexpected and difficult to demonstrate:

Demonstrating the absence of a tendency to polymorphism is not easy; most substances when investigated for a sufficiently long time will reveal more than one polymorph [42].

302. Therefore, it would have been reasonable to expect a given compound to follow this general rule, including sorafenib tosylate.

303. In 1990, Borka and Haleblan had published an extensive list of over 470 pharmaceutically important compounds that exhibited polymorphism. *See* Laszlo Borka and John K. Haleblan, "Crystal Polymorphism of Pharmaceuticals," *Acta Pharm. Jugosl.*, 40, 71-94 (1990). In Chapter 7 of his book, *Polymorphism in Molecular Crystals*, Bernstein cites this

²²⁹ Caira (1998), citing McCrone (1965).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

paper as well as other large compilations of pharmaceutical crystal forms, including that of over 559 crystal forms reported by Griesser and Burger in 1999. Clearly, by 2002, when this book was published, those in the pharmaceutical field were well aware of the prevalence of polymorphism. Raw also teaches that identification of polymorphs is important in the pharmaceutical industry:

Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences, which may result in product development delay and commercial production... As a result, pharmaceutical solid polymorphism has received much scrutiny throughout various stages of drug development, manufacturing, and regulation. For these reasons, it is essential that during drug product development and ANDA regulatory review, close attention be paid to pharmaceutical solid polymorphism.

Raw, *et al.*, “Regulatory Considerations of Pharmaceutical Solid Polymorphism in Abbreviated New Drug Applications (ANDAs),” *Adv. Drug. Deliv. Rev.*, 56, 397-414 (2004) at 400.

304. In “Thermal analysis and calorimetric methods in the characterization of polymorphs and solvates,” *Thermochimica Acta*. 248, 1-59 (1995) at 3) (“Giron (1995)”), Giron states that “Investigating the polymorphic behavior of drugs and excipients is an important part of preformulation work.” Giron (1995) also provides an extensive list of polymorphism and pseudo-polymorphism found in the literature.

(ii) A POSA Would Have Been Motivated to Search for Polymorphs

305. Given that many compounds commonly exhibit polymorphism, the skilled artisan would have been motivated to determine whether sorafenib tosylate can exist in multiple polymorphic states in order to exploit potentially favorable properties of one polymorph versus others, and would not have found it unexpected that sorafenib tosylate does exhibit polymorphism.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

306. The purpose of FDA Guideline 1987 is to provide applicants with acceptable procedures for complying with regulations regarding the production of new drug substances, specifically, drug substances manufactured by chemical synthesis. *See* FDA Guideline 1987 at 1. FDA Guideline 1987 teaches that the quality and purity of the drug substance cannot be assured solely by end-of-the-line testing, but depends on proper control of the manufacturing and synthetic process as well. *See id.* at 2. FDA Guideline 1987 further teaches that a particular synthetic pathway will typically be uniquely associated with a set of impurities. *See id.* at 4. As set forth in the FDA Guideline 1987, FDA’s “regulations [for the manufacture of drug substances] require specifications and analytical methods ... to help assure that the proper identity, strength, quality, and purity of the drug substance have been attained and are consistent from batch to batch.” *Id.* at 25. With respect to impurities, FDA Guideline 1987 states that “[i]mpurities should not only be detected and quantitated, but should also be identified and characterized when this is possible with reasonable effort” and that “[a]ll major impurities should be individually limited.” *Id.* at 26-27.

307. The 1987 FDA guidelines were later updated to the ICH Q6A Guidelines (adopted by the FDA), which similarly applicants with acceptable procedures for complying with regulations regarding the production of new drug substances manufactured by chemical synthesis.

The guidelines explain:

Polymorphism may also include solvation or hydration products (also known as pseudopolymorphs) and amorphous forms. Differences in these forms could, in some cases, affect the quality or performance of the new drug products. In cases where differences exist which have been shown to affect drug product performance, bioavailability or stability, then the appropriate solid state should be specified.²³⁰

²³⁰ ICH Q6A Guidelines at 8.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

308. The ICH Q6A Guidelines also include four decision trees. It states:

Decision trees #4(1) through 4(3) provide additional guidance on when, and how, polymorphic forms should be monitored and controlled.

Note: These decision trees should be followed sequentially. Trees 1 and 2 consider whether polymorphism is exhibited by the drug substance, and whether the different polymorphic forms can affect performance of the drug product.²³¹

309. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

310. A polymorphism screen was conducted automatically at Bayer. Dr. Grunenberg testified that “all the colleagues involved in chemical development, they automatically transferred a part or partial quantity of their first developed active ingredients to me. They did

²³¹ ICH Q6A Guidelines at 9.

²³² [REDACTED]

[REDACTED]

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER**(iii) Regulatory and Industry Realities**

311. Because sorafenib tosylate was a drug candidate (and human use was claimed in the double patenting references), a POSA would have been motivated by regulatory requirements in the United States and other countries, and the realities of pharmaceutical development to attempt to identify the most stable polymorph.²³⁷ In fact, because Bayer was already seeking regulatory approval in the United States, a POSA would have assumed that Bayer had already conducted a polymorph study, had already identified the most stable form and likely selected it for use in its product. This is consistent with Bayer's own statements to the FDA.²³⁸

312. The 1987 FDA Guidelines explicitly teaches that "[a]ppropriate analytical procedures should be used to determine whether (or not) polymorphism occurs." 1987 FDA Guideline at 34. Thus, the 1987 FDA Guidelines do instruct an applicant to search for crystalline forms of a compound. *See, e.g.,* H. G. Brittain, "Spectral Methods for the Characterization of Polymorphs and Solvates," *J. Pharmaceutical Sciences*, 86(4), 405-412 (April 1997) at 405 ("A full evaluation of possible variations in crystallography that might be encountered is now essential for the development for a new drug compound because the Food and Drug Administration (FDA) requires that analytical procedures be used to detect polymorphic, hydrated, or amorphous forms of the drug substance. A series of flow charts and decision trees have been presented that are to be used by investigators seeking to characterize the crystallography of compounds under development for registration with regulatory authorities.")

²³⁶ [REDACTED]

²³⁷ *See* FDA Guideline 1987; ICH Q6A Guidelines; FDA Guideline 2000

²³⁸ BAYER_NEXAVAR_00102004 – 23 at BAYER_NEXAVAR_00102008.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

313. The ICH Q6A Guidelines and FDA December 2000 Guidelines are even more direct. As noted above, the very first step of the relevant decision tree is “Conduct polymorphism screen on drug substance”²³⁹

314. Different forms of molecular solids, including crystalline polymorphs, crystalline solvates, and amorphous materials, display unique properties, many of which could affect the compound’s performance as a pharmaceutical. For example, forms may vary in terms of chemical properties such as solubility, dissolution rate, and bioavailability, as well as bulk properties, such as chemical stability, ease of filtering and drying, and flowability. *See* Threlfall (1995) at 2436. For example, polymorphs of the diabetes drug chlorpropamide have very different dissolution profiles and crushing strength, properties that affect both the administration and manufacture of this and other pharmaceuticals. *See* Byrn (1999) at 178, 274. Thus, the discovery or preparation of a polymorph or new polymorphs of a known compound is an important consideration for drug development. The strong motivation for drug companies to discover polymorphs has been recognized in the literature. *See, e.g.,* Bernstein (2002) at 27, 255, 297-298; *see also* Guillory (1999) at 184-185.

315. Beginning in 1987, the FDA’s Guidelines For Submitting Supporting Documentation In Drug Applications For The Manufacture Of Drug Substances required polymorph screening and identification for solid dosage forms or suspension drug products. In particular, the Guidelines state:

316. A person of ordinary skill in the art would understand that FDA’s Guidelines:

[r]egulations require, where appropriate, specifications characterizing the drug substance so as to assure the bioavailability of the drug product (*see* 21 CFR 314.50(3)(ii), and 320.52(e) [4-

²³⁹ ICH Q6A Guidelines at 24.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

1-85 edition])). Certain solid-state properties of the drug substance (e.g., polymorphic form or amorphism, solvation or hydration, various types of inclusion complexes, and particle size or surface area) may profoundly affect dissolution and bioavailability from solid dosage forms or suspension drug products.

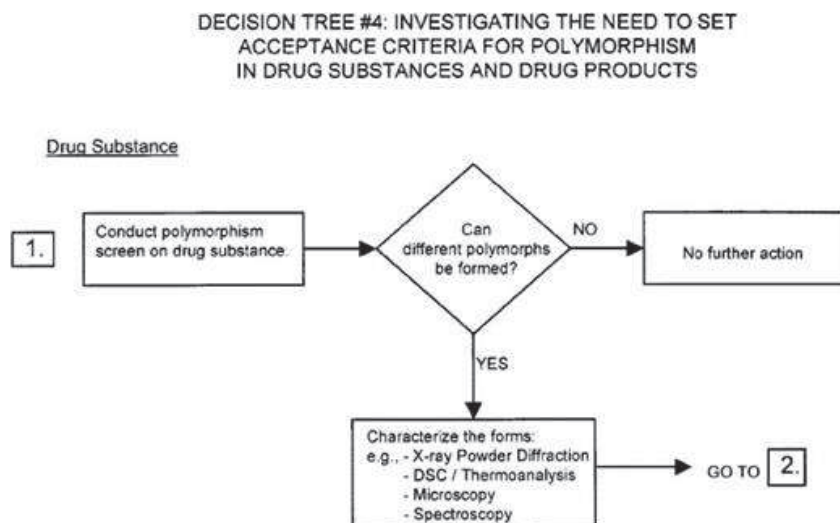
FDA Guideline 1987 at 31. The FDA goes on to instruct that “[a]ppropriate analytical procedures should be used to determine whether (or not) polymorphism occurs.” *Id.* at 34. The FDA required drug products to be designed to guarantee that the solid-state form would not change. In particular, FDA states that information should be provided to ensure that:

- (a) a change in solid-state form does not occur when the drug substance is manufactured and stored according to the NDA directions; or]
- (b) different forms occur but do not result in a bioavailability problem; or
- (c) polymorphism, solvation, or particle size has an important effect on bioavailability.

FDA Guidelines 1987 at 33.

317. In addition, the FDA guidance from December 2000 explained that “[d]ifferences in these [polymorphic] forms could, in some cases, affect the quality or performance of the new drug products.” *See* FDA Guidance on Q6A Specifications, 65 Fed. Reg. 251, 83046 (Dec. 29, 2000); *see also* ICH Harmonised Tripartite Guideline, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances Q6A (1999) at 8. These guidelines mention drug product stability and bioavailability as areas where different polymorphic forms could cause different results. *See* FDA Guidance on Q6A Specification (2000) at 83046; ICH Guideline Q6A (1999) at 8.

318. The FDA Q6A Specification specifically recommends that applicants conduct a polymorphic screen as the first step in investigating the need to set acceptance criteria for

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

polymorphism in drug substances. *See* FDA Guidance on Q6A Specification (2000) at 83046, 83055; ICH Guideline Q6A (1999) at 8-9, 24.

319. Cairra notes the regulatory requirement of pharmaceutical manufacturers to provide evidence for the occurrence or absence of polymorphism in a given product. Cairra states:

Already, legislation requiring drug manufacturers to provide information relating to the occurrence (or apparent absence) of polymorphism in their products has been introduced. Demonstrating the absence of a tendency to polymorphism is not easy; most substances when investigated for a sufficiently long time will reveal more than one polymorph.

Cairra (1998) at 166 (citations omitted). Cairra also states: “A recent analytical study stresses the growing need, prompted partly by legislative requirements, to differentiate polymorphs and to quantify polymorphic mixtures in pharmaceutical production.” Cairra at 189 (citation omitted).

320. Threlfall (1995) echoes these sentiments:

Much of the literature on polymorphism of organic compounds relates to pharmaceutical products. The incentive for this interest in polymorphism began with the need to satisfy regulatory authorities in various countries as to the bioavailability of formulations of new chemical entities.

Threlfall (1995) at 2436.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

321. Byrn notes that “[i]nterest in the subject of pharmaceutical solids stems in part from the Food and Drug Administration’s (FDA’s) drug substance guideline that states ‘appropriate’ analytical procedures should be used to detect polymorphic, hydrated, or amorphous forms of the drug substance. These guidelines suggest the importance of controlling the crystal form of the drug substance.” Stephen Byrn, et al., “Pharmaceutical Solids: A Strategic Approach to Regulatory Considerations,” *Pharm. Res.*, 12(7), 945-954 (1995) at 945 (“Byrn (1995)”).

322. Vippagunta notes that:

Because different crystalline polymorphs and solvates differ in crystal packing, and/or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physical properties, such as density, hardness, tableability, refractive index, melting point, enthalpy of fusion, vapor pressure, solubility, dissolution rate, other thermodynamic and kinetic properties and even color. Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products, while differences in solubility may have implications on the absorption of the active drug from its dosage form, by affecting the dissolution rate and possibly the mass transport of the molecules. These concerns have led to an increased regulatory interest in understanding the solid-state properties and behavior of drug substances. For approval of a new drug, the drug substance guideline of the US Food and Drug Administration (FDA) states that “appropriate” analytical procedures need to be used to detect polymorphs, hydrates and amorphous forms of the drug substance and also stresses the importance of controlling the crystal form of the drug substance during the various stages of product development. It is very important to control the crystal form of the drug during the various stages of drug development, because any phase change due to polymorph interconversions, desolvation of solvates, formation of hydrates and change in the degree of crystallinity can alter the bioavailability of the drug. When going through a phase transition, a solid drug may undergo a change in its thermodynamic properties, with consequent changes in its dissolution and transport characteristics.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Sudha R. Vippagunta, et al., “Crystalline Solids,” *Adv. Drug Deliv. Revs.*, 48, 3-26 (2001) at 4-5 (citations omitted).

323. Further, Beckmann wrote in 2000:

As concerns the pharmaceutical industry, it has been shown that more than half of the drug substances described in monographs crystallise in more than one solid state form, being it either polymorphs, solvates, or both. The solid state form of a drug substance can influence a variety of properties, namely the solubility and rate of dissolution or the chemical stability or stability against excipients. Thus, the regulatory bodies require an exhaustive search for polymorphic forms of a drug substance.

Wolfgang Beckmann, “Seeding the Desired Polymorph: Background, Possibilities, Limitations, and Case Studies,” *Organic Process Research & Development*, 4, 372–383 (2000) at 372.

324. This is consistent with Plaintiffs’ own experience

(iv) Need to Understand the Energy Landscape

325. A POSA also would have been motivated to search for the most stable polymorph in general in order to understand the energy landscape of the sold forms of the compound. *See*, e.g., Grunenberg (1996) .

326. In his 2002 book, “Polymorphism in Molecular Crystals,” Bernstein highlights the importance of screening a compound for polymorphic behavior and the necessity of understanding the energy landscape for both the stable and metastable forms that one is able to generate.²⁴⁰ This alone would provide more than enough motivation for one skilled in the art to initiate a solvent screen and other methods designed to find as many polymorphs of sorafenib tosylate as possible.

The lower solubility of stable forms may limit their pharmacological utility (e.g. ritonavir (Chemburkar *et al.* 2000; Bauer *et al.* 2001)), so that it may be advantageous to selectively

²⁴⁰ Bernstein (2002) at 252-253.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

obtain and maintain a metastable form in a formulation (e.g. Shah *et al.* 1999). In such cases, crystallization strategies may be designed on the basis of the principles derived from the energy-temperature or pressure-temperature diagrams (Toscani 1998), as described in Chapter 3. It will be recalled that even if qualitative in many aspects, such diagrams serve to summarize a great deal of information in a very compact manner. For instance, characterization of the two polymorphs of taltireline, a central nervous system activating agent, indicated that they were enantiotropic, but the α form, metastable at its crystallization temperature of 10° C, was preferred for formulation. Critical evaluation of the crystallization parameters isolated the factors that led to conversion of the stable form, and these were controlled to prevent conversion (Maruyama *et al.* 1999). For a two-component system generation of the phase diagram can also prove very useful in developing strategies for obtaining a number of crystal modifications, including a metastable one (Henck *et al.* 2001).

Together with knowledge of the phase diagram an increasing variety of techniques have been designed and employed to generate metastable modifications. Seeding of course, is one of those strategies, and Beckmann *et al.* (1998) developed a seeding strategy for a batch cooling crystallization to obtain quantitatively and reproducibly a metastable form of abecarnil, regardless of the purity of the material. In another approach, after thorough characterization of three polymorphic modifications by a variety of analytical methods, a desired metastable form of (R, S)-proxyphylline was crystallized in gram quantities from the supercooled melt, and proved to have considerable kinetic stability under dry atmospheric conditions (Griesser *et al.* 2000). A variation on that same theme was the successful high-temperature crystallization from the amorphous material of the metastable α form of indomethacin, whereas the low temperature crystallization yielded the stable γ form (Andronis and Zografi 2000).

One traditional strategy for screening a compound for polymorphic behaviour involves the trial of a variety of solvents and solvent mixtures. Our understanding of the role and choice of solvent has improved considerably and this information, combined with a knowledge of zones of stability can aid in determining crystallization conditions for obtaining metastable form (Threlfall 2000). In addition, there has also been considerable progress in understanding and utilizing the interactions of solvent with the growing crystal (Weissbuch *et al.* 1991; Lahav and Leiserowitz structure determinations of polymorphs with crystal morphological data (i.e. crystal habit, and the orientation of molecules projecting

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

from the particular faces exposed) and with known intermolecular interactions between solute molecules and solvent functional groups allows the rational choice of solvent to select a particular polymorphic form (Weissbuch et al. 1995). An analysis of this nature was carried out and experimentally confirmed by Blagden et al. (1998a, b) for polymorphic modification of sulphathiazole.

This is clearly an area where the combination of thermodynamic, kinetic and structural information potentially can lead to successful strategies for controlling the polymorphic form obtained, in specific instances a metastable form, and as the means for obtaining these data become more sophisticated the approaches described here are sure to be developed and expanded (*See also* Section 3.7).²⁴¹

327. Giron (2004) also states:

Precise knowledge of thermodynamic stability and relationships between different solid phases is a pre-requisite for the manufacture of robust drug substance and drug products. It is also necessary to know the equilibration curves between the solid forms under the influence of the parameters humidity, temperature and pressure in order to predict changes for storage, stability, compatibility and pharmaceutical processes. The major hurdle for the pharmaceutical industry is to have to recall medicines because of polymorphism problems as it was the case for Ritonavir.

Giron (2004) at 710.

328. This industry experience with ritonavir was one of the reasons Dr. Grunenberg recommended use of the most stable polymorphic form.²⁴²

(v) A POSA Would Have Been Specifically Motivated to Use Thermal Evaluation Techniques

329. [REDACTED]

[REDACTED] Thermal techniques including hot stage or thermal microscopy, DSC, and TGA have

²⁴¹ Bernstein (2002) at 252-253 (emphasis added).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

been employed for decades in the pharmaceutical industry to assess transitions between crystal forms.²⁴⁴

330. Byrn provides the following flowchart/decision tree, which specifically identifies DSC and other thermoanalytical methods as part of the standard process of polymorph identification.²⁴⁵

²⁴⁴ Byrn (1999) at 279; Caira (1998) at 178; Halebian at 918; Threlfall (1995) at 2439, 2446.

²⁴⁵ Byrn (1995) at 949.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

POLYMORPHS

Drug Substance

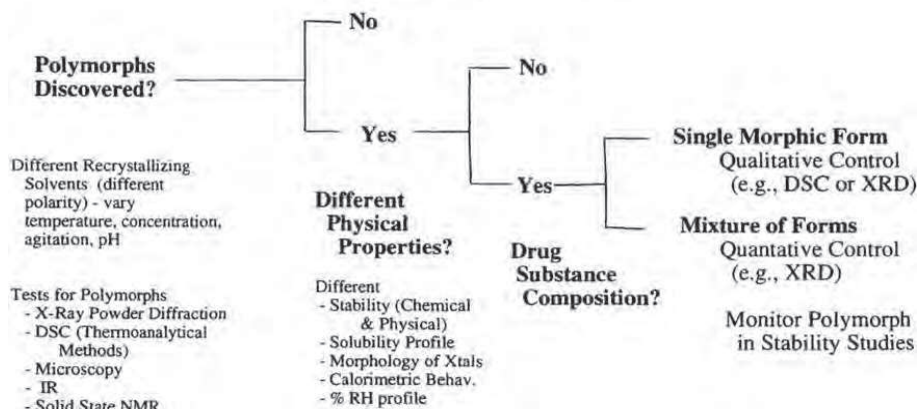


Figure 1. Flow chart/decision tree for polymorphs.

HYDRATES (SOLVATES)

Drug Substance and Solvent

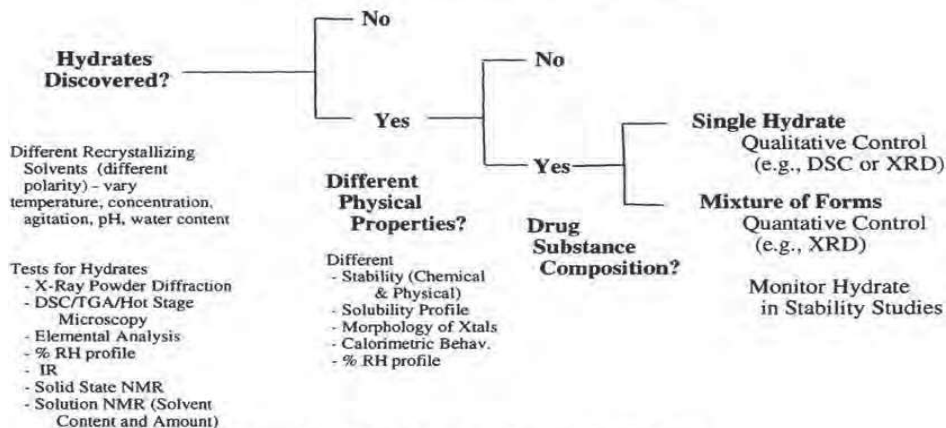


Figure 6. Flow chart for solvates or hydrates.

331. Based on the knowledge of a POSA, as exemplified in the literature references discussed above, it would have been obvious to a POSA to use melting point, hot-stage microscopy, DSC, or TGA to assess the relative thermal stability of any crystal form that he or she prepared. This would have inevitably produced Polymorph I.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

(a) Melting point

332. One method of characterizing crystal forms is by taking a melting point. It is often possible to distinguish two polymorphic forms by their melting points, especially when the melting points are well separated.²⁴⁶

(b) Hot-Stage Microscopy

333. Hot-stage microscopy has been employed for decades in the pharmaceutical industry to assess transitions between crystal forms. In this method, the sample is heated gradually on a microscope stage while events are recorded visually or with either photographs or videos. This is a convenient technique that allows a scientist to visually observe and record phase changes as a function of temperature. Hot-stage microscopy is often used in conjunction with differential scanning calorimetry (“DSC”).

334. Threlfall recognizes that hot stage microscopy is a technique for generating polymorphs. In particular, he states: “hot-stage microscopy has been often so used and remains the outstanding method for the examination and generation of polymorphs.” Threlfall (1995) at 2439. He further states:

A preliminary examination under a binocular microscope will enable the overall characteristics of the sample to be ascertained. Temperature cycling and melt and solvent recrystallization experiments with a polarizing microscope equipped with a hot-stage will allow the identification of transition points, the distinguishing of monotropic and enantiotropic relationships, estimation of the tendency of melts and individual phases to supercool, ***the generation of stable and unstable polymorphs*** and the recording of their optical properties. The identification of solvates and the observation of sublimates and of any tendency to decompose are added information. This can be carried out with minute amounts of material. The field has been excellently and

²⁴⁶ See, e.g., Giron (2002) at p. 50; Giron (2004) at p. 727.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

comprehensively reviewed in the past, and for that reason only the developments since then will be considered in detail here.²⁴⁷

Thus, hot stage microscopy is an important tool for investigating polymorphism of crystalline solids.

(c) Differential Scanning Calorimetry (“DSC”)

335. Differential Scanning Calorimetry (“DSC”) is a type of test that can be used to measure the melting point of a material. DSC uses the thermal characteristics of different phase transitions to distinguish between different materials. In DSC, one applies enough thermal energy (or power) to the sample and a reference to keep them at the same temperature while warming or cooling. The DSC data is in the form of a curve showing the heat flow as a function of sample temperature. The direction of the peak (which is either endothermic or exothermic) helps to identify the type of transformation taking place.

336. The DSC trace complements the melting point by providing detailed information about the melting transition, including the enthalpy of fusion (i.e., the heat energy that must be added to melt a specific amount of the substance), which is a characteristic property of each crystalline form. The DSC can provide diagnostic information related to pre-melting behavior, phase transitions, decomplexation of bound solvent, and chemical decomposition.

337. In particular, DSC is used throughout the pharmaceutical industry to identify new crystalline forms of drug substances. Both desolvation and solid-solid phase transformations

²⁴⁷ Threlfall (1995) at 2439 (emphasis added); *See also* Byrn (1999) at 279; Caira (1998) at 178; Halebian (1969) at 918.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

give rise to signals in the DSC trace and would prompt further investigation of the crystal forms generated by these thermal processes.²⁴⁸

(d) Thermogravimetric Analysis (“TGA”)

338. In a thermogravimetric analysis (or thermogravimetry), the mass of a compound is monitored as a function of temperature. Typically, a known amount of sample is heated at a constant rate, and the loss of mass due to decomposition or evaporation is recorded as a function of time while an inert gas is flowed past the sample. Both the mass of the sample and the first derivative (mass loss per temperature unit) are plotted as a function of temperature.

339. As described above, thermal evaluation techniques inevitable would have produced Polymorph I.

(vi) A POSA Would Have Been Specifically Motivated to Conduct a Polymorph Screen and Motivated to Identify the Most Stable Polymorph

340. A POSA would have been motivated to seek the most stable polymorphic form of sorafenib tosylate because that form would be unlikely to convert to a different polymorphic form that could negatively impact a drug product’s quality or performance.²⁴⁹

341. During the prosecution of the corresponding European patent, Plaintiffs stated:

It is very important for a pharmaceutical product to have always the same constant properties. Therefore there is a need to find the most stable form of a compound because only the most stable form can ensure that all properties and characteristics regarding stability, solubility, shelf life and bioavailability maintain constant during manufacturing, storage and administration. . . . The metastable forms have different shelf lives, solubilities and bioavailabilities and due to its metastability they have the tendency to change into different forms having different properties. For a pharmaceutical

²⁴⁸ See, e.g., E. Shami, et al., “Preformulation” in *Theory and Practice of Industrial Pharmacy* (1976) at 4 (“Shami (1976)”) (worksheet for summarizing data, and noting melting point and DSC in particular).

²⁴⁹ See MYL_SOR00011392 – 393.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

product it is important to have always the same constant properties.
Only the stable form according to the present invention can ensure
these constant properties.²⁵⁰

342. Plaintiffs also wrote:

Since pharmaceutical compositions shall have the same reliable
form for the active ingredient having the same reliable and
constant properties, there is the need to use the stable
polymorph.²⁵¹

343. And Plaintiffs reported their polymorphism examinations to the FDA.²⁵²

344. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

345. [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

²⁵⁰ [REDACTED]

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

[REDACTED]

346. There are numerous references that demonstrate motivation and knowledge. For example, in his chapter entitled, “Preformulation,” Fiese, et al., states:

During preformulation, it is important to identify the polymorph that is stable at room temperature and to determine whether polymorphic transitions are possible within the temperature range used for stability studies and during processing (drying, milling, etc.).²⁵⁷

347. Cairra explains that when developing a new drug product, “[s]ystematic investigation of a compound to determine whether it is prone to polymorphism . . . *is routine practice* in pharmaceutical pre-formulation studies. Identification of the different polymorphic forms of a drug substance . . . [is] essential for ensuring drug preparations with reproducible behaviour.”²⁵⁸

348. Similarly, Guillory explains that “[i]t is incumbent on the manufacturer of a new drug substance to show that due diligence has been employed to isolate and characterize the various solid-state forms of a new chemical entity.”²⁵⁹

349. Threlfall further explains:

As formulations have become more sophisticated and as the tolerances on products have become tighter, the need to identify polymorphic behaviour at an early stage of development has become important in the pharmaceutical industry as a means of ensuring reliable and robust processes and conformity with good manufacturing practice. The aim is to avoid, *inter alia*, tableting problems and subsequent tablet failure, crystal growth in suspensions and resultant caking, precipitation from solutions and problems with suppositories, as well as chemical production

²⁵⁶ [REDACTED]

²⁵⁷ Eugene F. Fiese, et al., Chapter 8 in *The Theory and Practice of Industrial Pharmacy*, Lachman, et al., Eds., Lea & Febiger, 171-96 (1986) at 180-81.

²⁵⁸ Cairra (1998) at 165-66.

²⁵⁹ Guillory at 185.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

problems such as filtrability and to ensure analytical reproducibility.²⁶⁰

350. Byrn provides further motivation to conduct studies of polymorphism of pharmaceuticals in section 13.3 of his book at 266-278. Byrn (1999). Here, he cautions the reader that changes in polymorphic form might affect the solubility and bioavailability of the pharmaceutical:

13.3 POLYMORPHIC TRANSFORMATIONS OF PHARMACEUTICALS

In this section, studies of drugs that undergo polymorphic transformation are reviewed and discussed. This is an important area of research because of its implications in the physical stability of drug dosage forms. As mentioned earlier, different polymorphs possess different physical properties-solubility and bioavailability being the most important. In addition, keep in mind that changing the temperature or pressure during a manufacturing operation, such as tableting, could induce a polymorphic transformation.²⁶¹

351. The vast majority of drugs use the most stable form of the drug as the commercial active pharmaceutical ingredient. In the context of pharmaceuticals, the most stable polymorphic form is a preferred form, because, for example, it can extend the shelf life of the drug.²⁶²

352. The most stable form is most frequently chosen for commercial development because of risk of conversion.

The goal in any industrial pharmaceutical organization is to have the thermodynamically preferred polymorph or solvate present in the first scaled-up batch of drug substance. If this situation is achieved, then all toxicology, pharmacokinetic, and clinical studies will be conducted with the crystalline form that is likely to be the commercial form of the drug substance. This will eliminate expensive retesting should a more stable but previously unknown

²⁶⁰ Threlfall (1995) at 2436.

²⁶¹ Byrn (1999) at 266. *See also* Shami (1976) at 3 (“Investigating the polymorphic properties is important, since polymorphic forms in many cases exhibit differences in biological availability.”).

²⁶² Halebian (1969) at 912-13; MYL_SOR00012740 – 962 at MYL_SOR00012929.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

polymorph appear. Prudent drug development programs will identify the preferred crystalline form early in development, with a polymorph/salt group working in close conjunction with process chemists to make the thermodynamically preferred polymorphic form the initial kilogram-scale batch. They will also identify and define the physicochemical boundaries of that polymorph.²⁶³

353. Accordingly, the goal of understanding the thermodynamic relations between the different crystal forms, and in particular the relation of other forms to the most thermodynamically stable polymorphic form of a drug substance, is a significant consideration during drug product development.

354. Caira cites safety reasons for the control of crystal form used in pharmaceuticals:

Solubility and dissolution rate analyses are of vital importance for polymorphs and pseudopolymorphs of pharmaceutical relevance. For a given drug, metastable polymorphs tend to have higher solubilities and faster dissolution rates than the stable polymorph. When metastable forms are employed in solid dosage forms (tablets, capsules), they generally yield higher and earlier blood serum levels. Thus, for potent drugs with a narrow therapeutic index (*e.g.* the cardiotonic digoxin), inadvertent use of a metastable polymorph in a tablet could result in patient death from overdose. In vitro dissolution testing is therefore carried out routinely as part of the quality control of manufactured tablets and capsules.²⁶⁴

355. Guillory urges early assessment of the relative stabilities of different crystal forms because of the possibility of conversion from a metastable form to a more stable one:

It is essential to ascertain whether the crystalline material that results from a synthetic procedure is thermodynamically stable before conducting pivotal trials, since a more stable form may be obtained subsequently, and it may be impossible to produce the metastable form in future syntheses. Conversion from one

²⁶³ Harry G. Brittain and Eugene F. Fiese, "Effects of Pharmaceutical Processing on Drug Polymorphs and Solvates," Ch. 8 in *Polymorphism in Pharmaceutical Solids*, Harry G. Brittain, Ed., Marcel Dekker, Inc., New York, NY, 331-361 (1999) at 358.

²⁶⁴ Caira (1998) at 191.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

polymorph to another can occur during processing or upon storage.²⁶⁵

356. Repeating these same principles, Yu explains that:

The widespread existence of polymorphic drugs underscores the importance of an efficient and consistent characterization strategy. The potential impact of changing crystal forms during late-stage development in terms of cost and product delay justifies the systematic and early characterization of polymorphism.²⁶⁶

357. It was known in the art as of the priority date that polymorph screening was necessary to ensure consistent, bioavailable, and stable drug product, as Plaintiffs themselves admitted. It was also known that the consequences of not investigating the relative stabilities of different crystal forms and their ease of conversion could be devastating, both for the manufacturer, and, in some cases, for public health. In 1996, Abbott Laboratories began to market a semi-solid capsule of ritonavir (NorvirTM), which was an important protease inhibitor used in the fight against HIV/AIDS. Because of its low bioavailability and low solubility, ritonavir was formulated in an ethanol/water solution. In 1998, after 240 lots had been produced without any solubility problems, certain capsules began to fail the dissolution tests as a new, more stable polymorph emerged.²⁶⁷ Soon thereafter, it was no longer possible to generate the original metastable form as “seeds” of the more stable form infiltrated laboratories and manufacturing plants.²⁶⁸ The sudden appearance of this stable form of ritonavir and the great

²⁶⁵ Guillory (1999) at 184.

²⁶⁶ See Lian Yu, et al., “Physical characterization of polymorphic drugs: an integrated characterization strategy,” PSTT, 1, 118-27 (1998) at 125-26 (“Yu (1998)”).

²⁶⁷ Sanjay Chemburkar, et al., “Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development,” *Organic Process Research & Dev.*, 4, 413-417 (2000) at 413 (“Chemburkar (2000)”).

²⁶⁸ *Id.* at 416-17.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

difficulty in manufacturing the metastable form required Abbott to remove ritonavir from the market for over a year as it searched for a new formulation.²⁶⁹

358. The prior art experience with ritonavir presents a cautionary tale that the pharmaceutical industry has taken to heart. Chemburkar (from Abbott) writes: “It is highly advisable to put enough resources to carry on exhaustive research to identify the most stable and all possible polymorphs.”²⁷⁰

359. Thus, a POSA as of the priority date would have been keenly aware of the necessity of performing a polymorph screen and identifying the most thermodynamically stable polymorph of a drug substance such as sorafenib tosylate.

360. A POSA would therefore have been specifically motivated to attempt to identify the most stable polymorph of sorafenib tosylate.

(vii) Solution-Mediated Transformations and “Slurrying”

361. As noted above, a POSA would have been motivated to find the most stable form of sorafenib tosylate for pharmaceutical development.

362. In practice, the simplest and most typical way of searching for the most stable crystal form involves a “slurry conversion,” in which the different crystal forms of a particular compound are rapidly stirred over a period of hours or days in the presence of solvent sufficient to dissolve only a small amount of the substance in question.²⁷¹

²⁶⁹ *Id.*; see also J. Bauer, et al., “Ritonavir: An Extraordinary Example of Conformational Polymorphism,” *Pharmaceutical Research*, 18(6), 859-866 (2001) (“Bauer (2001)”).

²⁷⁰ Chemburkar (2000) at 417. See also Bauer (2001) at 859 (noting that because ritonavir was in ethanol/water solution “no crystal form control was required” under the then-operative ICH guidelines). This, of course, had devastating consequences that the industry has heeded.

²⁷¹ Halebian (1969) at 922.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

363. Because the most thermodynamically stable polymorph generally has the lowest solubility, this process, which typically involves dynamic dissolution and recrystallization, can be used to convert less stable polymorphs into the most thermodynamically stable polymorph.²⁷² A POSA would understand that a reliable way of identifying the most stable crystal form of sorafenib tosylate would be to slurry any of the solid forms that might be generated in several different solvents and to compare the results of these slurries by using powder X-ray diffraction.²⁷³ (“An efficient method to discover the most stable polymorph is the technique of solvent-mediated polymorphic transformation.” (Gu (2001)) at 1878-1879.)

364.

365. Caira cites earlier literature on solvent-mediated transformations, whose driving force is the difference in solubility between different forms:

Theoretical and experimental studies of the role of solvent on polymorphic crystallization and phase transformations abound in the literature of the last few years and some pertinent examples are described here. For solvent-mediated transformations, the driving force is the difference in solubility between different polymorphs. An important earlier paper on the kinetics of such phase transformations described a model featuring two kinetic processes in solid to solid phase changes via a solution phase, namely dissolution of the metastable phase and growth of the stable one.²⁷⁴

366. Grant also discusses the use of solution-mediated phase transformations of metastable polymorphs to give more stable ones:

²⁷² Threlfall (1995) at 2449 (“The solubility also has an important thermodynamic feature: it is inversely related to the stability of the polymorph such that the most stable polymorph is always the least soluble at a given temperature.”).

²⁷³ See, e.g., Chong-Hui Gu, Victor Y. Young, and Gavid J. W. Grant, “Polymorphic Screening: Influence of Solvents on the Rate of Solvent-Mediate Polymorphic Transformation,” *Journal of Pharmaceutical Sciences*, 90(11), 1878-1890 (2001) (“Gu (2001)”).

²⁷⁴ Caira (1998) at 169.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Under appropriate thermodynamic conditions discussed at the beginning of this chapter, a less stable polymorph may be converted into a more stable polymorph. The rate of conversion to the more stable polymorph is often rapid, if mediated by the solution phase or vapor phase. In these phases the less stable polymorph (having the greater solubility or vapor pressure) dissolves or sublimes, while the more stable polymorph (having the lower solubility or vapor pressure) crystallizes out.²⁷⁵

367. Rodriguez-Hornedo provides the same sentiments:

Knowledge of the propensity of a metastable solid phase to dissolve in a liquid phase from which a stable solid phase nucleates and grows is crucial in many stages of pharmaceutical development, because pharmaceutical solids are designed to be dissolved and to come in contact with solvents since the early stages of development (isolated by crystallization from solution) and during processing (wet granulation, spray-drying, freeze-drying, etc.). Given that the sudden disappearance or appearance of a crystalline modification can threaten process development, characterization of the kinetics and mechanisms of solvent-mediated transformations is of practical importance.²⁷⁶

368. Guillory also explains that slurries result in the conversion from a metastable polymorph to a more stable one through a solution phase mediated transformation:

According to McCrone, in a poor solvent the rate of transformation of a metastable to a more stable polymorph is slower. Hence a metastable form once crystallized can be isolated and dried before it is converted to a more stable phase by solution phase mediated transformation.²⁷⁷

369. Kiyotaka Sato ("Polymorphic transformations in crystal growth," *J. Phys. D: Appl. Phys.*, 26, B77-B84 (1993)) writes:

²⁷⁵ Grant (1999) at 26.

²⁷⁶ Naír Rodríguez-Hornedo and Denette Murphy, "Significance of Controlling Crystallization Mechanisms and Kinetics in Pharmaceutical Systems," *J. Pharm. Sci.*, 88, 651-660 (1999) at 657.

²⁷⁷ Guillory (1999) at 193 (citing W. C. McCrone, "Polymorphism," Chapter 8 in *Physics and Chemistry of the Organic Solid State*, Vol. II (D. Fox, M. M. Labes, and A. Weissberger, Eds.), Interscience, New York, (1965)).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

The driving force of these transformations is the Gibbs energy difference between the polymorphs. Ostwald ripening is a well-known similar phenomenon. It dictates an achievement of a free energy minimum condition in a crystal-medium system consisting of a poly-disperse precipitate, governed by the difference in solubility between the poly-disperse crystal particles [21].

370. [REDACTED]

(viii) A POSA Would Have Been Motivated to Run a Standard Solvent Screen

371. A POSA also would have been motivated to run a standard polymorph screen using routine solvents and recrystallization conditions with a reasonable expectation of success to form crystalline solids.

372. In addition to the techniques discussed above, there are a number of standard techniques that scientists use to screen for polymorphs. In his book entitled, "Polymorphism in Molecular Crystals," Bernstein emphasizes the role of solvent screens in finding new polymorphic forms:

One traditional strategy for screening a compound for polymorphic behaviour involves the trial of a variety of solvents and solvent mixtures. Our understanding of the role and choice of solvent has improved considerably and this information, combined with acknowledge of zones of stability can aid in determining crystallization conditions for obtaining metastable form (Threlfall 2000). In addition, there has also been considerable progress in understanding and utilizing the interactions of solvent with the growing crystal (Weissbuch *et al.* 1991; Lahav and Leiserowitz (1993). Combining the detailed structural information available from the single crystal structure determinations of polymorphs with crystal morphological data (*i.e.* crystal habit, and the orientation of molecules projecting from the particular faces exposed) and with known intermolecular interactions between solute molecules and solvent functional groups allows the rational choice of solvent to select a particular polymorphic form

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

(Weissbuch *et al.* 1995). An analysis of this nature was carried out and experimentally confirmed by Blagden *et al.* (1998a, b) for polymorphic modification of sulphathiazole.

Bernstein (2002) at 252.

373. In his chapter entitled, “Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids” (*Polymorphism in Pharmaceutical Solids*, H. G. Brittain, Ed. (1999) at 184-202), Guillory describes a screening protocol that can be used by those in the pharmaceutical industry:

In this context, it is hoped that the following information will prove useful in devising a “screening” protocol for the preparation of the various solid state forms of pharmaceuticals. While one cannot be absolutely certain that no additional forms will be identified in the future, this approach should provide some assurance that “due diligence” has been exercised to isolate and identify crystalline forms that are likely to arise during the normal course of drug development and storage.

Guillory (1999) at 186.

374. In this case, Dr. Grunenberg conducted [REDACTED]

D. A POSA Would Have Had a Reasonable Expectation of Success in Identifying the Most Stable Polymorphic Form of Sorafenib Tosylate.

375. The most stable crystalline form of a compound is usually the most readily obtainable form. It would have been routine—and obvious—for a POSA to have obtained the most thermodynamically stable polymorphic form of sorafenib tosylate. For example, a POSA would have used any of the standard techniques to take a melting point of sorafenib tosylate, or their equivalent (DSC, hot bar, TGA, etc.) that would have inevitably produced Form 1.

²⁷⁹ Grunenberg [REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

376. As described above, a POSA would have, for example, slurried sorafenib tosylate in a number of solvents at ambient conditions and would have obtained Form 1 as the most stable polymorph.²⁸⁰

377. Therefore, as discussed above, a POSA would have had good reasons to conduct polymorphic screening for sorafenib tosylate (thereby obtaining Polymorph I) and would then have ascertained Polymorph I as the most thermodynamically stable polymorphic form among those generated.

XIII. CLAIMS 1-2 AND 28-29 ARE INVALID AS OBVIOUS

378. For the reasons set out above, Polymorph I was obvious because a POSA would have been motivated to run, for example, standard thermal and analytical techniques on any form of sorafenib tosylate, a routine solution-mediated transformation experiment (slurry experiment), or a solvent screen with a reasonable expectation of success to identify the most thermodynamically stable crystalline form of sorafenib tosylate. *See, e.g.,* Guillory (1999) at 191-192; *see also* Byrn (1999) at 274-277. Polymorph 1 was an inevitable result of such slurry experiments.

379. Also explained above, it was well known in the art that characterization of polymorphs of a solid drug substance was an important aspect of drug development, and a required part of the new drug approval process. *See, e.g.,* Guillory (1999) at 184-185; Byrn (1995) at 945; ICH Guidelines at 1, 8. Furthermore, it was well known in the art that the most thermodynamically stable polymorphic form of a drug substance was generally the preferred form for purposes of formulating the drug.²⁸¹

²⁸⁰ *See* Bernstein (2002) at 27, 255, 297-298; Gu (2001).

²⁸¹ *See, e.g.,* Chemburkar (2000) at 413-417; Byrn (1995) at 946-948; Guillory (1999) at 184-186; Gu (2001); S. L. Morissette, "High-throughput crystallization: polymorphs, salts, co-

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

380. Having identified Form 1 as the thermodynamically stable form using routine solvent screens and slurry experiments, a POSA would have been motivated to choose Form 1 as the active pharmaceutical ingredient for development.²⁸²

1. Claims 1-2 and 28-29

381. Claims 1-2 and 27-31 recite sorafenib tosylate Polymorph I and with properties such as specific PXRD reflections, Raman spectroscopy maxima, IR maxima, and melting point.

382. Each of these additional limitations are inherent properties of sorafenib tosylate Polymorph I. As a result, they add nothing to the invalidity analysis of these claims. Once Polymorph I of sorafenib tosylate was made, it possessed all of its inherent properties.²⁸³

383. Because Polymorph I is obvious, claims reciting these additional limitations are likewise obvious because the limitations are inherent in Polymorph I.

XIV. CLAIMS 1-2 AND 28-29 ARE INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

384. For the reasons set out above regarding anticipation and obviousness, it is also my opinion that claims 1-2 and 28-29 of the '933 patent are invalid for obviousness-type double patenting over claim 41 of U.S. Patents No. 7,351,834 ("the '834 patent") and claims 6-11 of the 8,618,141 ("the '141 patent"), both of which I am informed are commonly owned, licensed or assigned with the '933 patent and expire before it.

385. The '834 patent issued April 1, 2008. It expires January 12, 2020, according to the Orange Book. Each of the Asserted Claims of the '933 patent is invalid for obviousness-type double patenting over at least claim 41 of the '834 patent. Claim 41 is directed to: "A compound

crystals and solvates of pharmaceutical solids," *Advanced Drug Delivery Reviews*, 56, 275-300 (2004) at 275-278, 285-291.

²⁸² See Guillory (1999) at 188-191; Byrn (1995) at 946.

²⁸³ See, e.g., Zumdahl (1986).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

of claim 39 which is a tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea.” ’834 patent at 100:46-48. As noted above, this patent is available as prior art.

386. The ’141 patent issued December 31, 2013. It expires February 11, 2023, according to the Orange Book. Claims 6 and 10 are directed to:

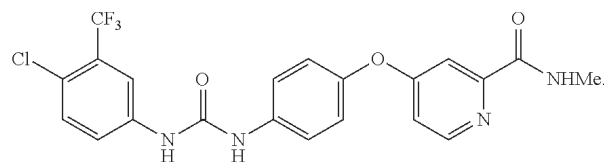
A method of blocking tumor angiogenesis in a human or other mammal comprising administering to a human or other mammal with a tumor of the breast, gastrointestinal tract, kidney, ovary or cervix, **an effective amount of the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea tosylate**

10. The method of claim 6, wherein the effective amount of the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea tosylate is between 0.01 to 200 mg/Kg of total body weight.

’141 patent at 40:36-41 (emphasis added), 41:5-8.

387. Claims 7-9 and 11 are directed to:

7. **A method** of blocking angiogenesis in a tumor of the kidney comprising administering to **a human** or other mammal with a tumor of the kidney an effective amount of the tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula below

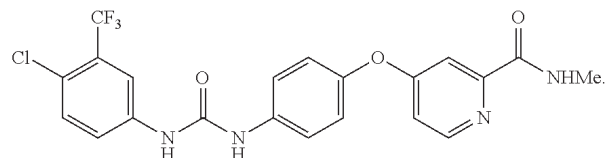


8. A method as in claim 7 wherein the tumor of the kidney that is treated is characterized by abnormal angiogenesis or hyperpermeability processes, which are not raf-mediated nor p38-mediated.

9. A method as in claim 8 wherein the tumor of the kidney that is treated is characterized by abnormal angiogenesis or hyperpermeability processes, which are mediated by KDR (VEGFR-2).

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

11. The method of claim 7, wherein the effective amount of the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula below is between 0.01 to 200 mg/Kg of total body weight



'141 patent at 40:42-41:4, 41:9-21 (emphasis added).

388. I note that that these claims are specifically directed to a method of using sorafenib tosylate “*in a human.*”

389. In order to practice the method of any of these claims in a human—as claimed in the '141 patent—a POSA would first have to meet regulatory guidelines, such as the FDA and ICH guidelines governing polymorphic forms.

XV. LACK OF INVENTORSHIP

390. It is also my opinion that neither Dr. Grunenberg nor Dr. Lenz are inventors of the ostensibly “inventive” Polymorph I, which is the only portion of the claims that is not disclosed in the prior art.

391. Polymorph I was first conceived and reduced to practice [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

392. Dr. Grunenberg testified [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

393. Dr. Riedl and his colleagues in the development labs [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

395. As result, nether Dr. Grunenberg nor Dr. Lenz can be inventors of the ostensible “inventive” Polymorph I, which is the key element of each of the claims of the ’933 patent.

XVI. SUPPLEMENTAL OPINIONS

396. In the even that Plaintiffs should submit any response to my report, I reserve the right to respond to any issues raised by that response, including expert reports.

397. I specifically reserve my right to provide additional opinions regarding secondary considerations of nonobviousness. I understand that under the Scheduling Order in this case, Defendants need not address evidence of secondary considerations in their opening round of expert reports; rather, secondary considerations shall be addressed by Plaintiffs in the second round of expert reports, and Defendants shall respond to such evidence in the reply round of expert reports.

398. If called to testify, my testimony may include an explanation of scientific principles that underlie the opinions expressed in this report.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

399. I have based my opinions and analyses on documents and information available to me at the time I signed the report. If and when any new evidence arises, I reserve the right to supplement or modify my opinions to reflect that evidence.

400. I reserve the right to prepare demonstratives to help explain my opinions.

HIGHLY CONFIDENTIAL PURSUANT TO PROTECTIVE ORDER

Dated this 13th day of April, 2017.

A handwritten signature in black ink, appearing to read "Mark D. Hollingsworth", is written above a horizontal line.

Mark D. Hollingsworth, Ph.D.

EXHIBIT 2

**EIN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

BAYER HEALTHCARE LLC, BAYER)	
HEALTHCARE PHARMACEUTICALS INC.,)	
and ONYX PHARMACEUTICALS, INC.,)	
)	
Plaintiffs,)	C.A. No. 15-114-LPS
)	(cons.)
v.)	
)	CONFIDENTIAL
MYLAN PHARMACEUTICALS INC.,)	
)	
Defendant.)	

**DEFENDANTS' FIRST SUPPLEMENTAL OBJECTIONS AND RESPONSES
TO PLAINTIFFS BAYER HEALTHCARE LLC, BAYER HEALTHCARE
PHARMACEUTICALS INC. AND ONYX PHARMACEUTICALS, INC.'S
FIRST SET OF INTERROGATORIES**

Pursuant to Rules 26 and 33 of the Federal Rules of Civil Procedure, Defendant Mylan Pharmaceuticals Inc. ("Mylan") hereby objects and responds to Plaintiffs Bayer Healthcare LLC, Bayer Healthcare Pharmaceuticals Inc., and Onyx Pharmaceuticals Inc.'s (collectively, "Plaintiffs") First Set of Interrogatories. These objections and responses are based on Mylan's current understanding, knowledge and belief. As discovery has just commenced and the case is in its early stage, Mylan's factual investigation and trial preparation is ongoing. Mylan reserves the right to supplement its responses as discovery progresses in this action.

GENERAL OBJECTIONS

Mylan makes the following General Objections to each Interrogatory:

1. Mylan incorporates by reference all objections set forth in the General Objections of Mylan's Responses to Plaintiffs' First Set of Requests for Production (Nos. 1-49).
2. Mylan objects to each Interrogatory to the extent it seeks information protected from disclosure by the attorney-client privilege, the work product doctrine, the common interest doctrine, or any other applicable privilege or immunity. Such information shall not be provided

in response to any Interrogatory and any inadvertent disclosure thereof shall not be deemed a waiver of any privilege with respect to such information, or of any work product protection, which may attach thereto.

3. In furnishing these objections and responses to these interrogatories, Mylan does not admit or concede the relevance, materiality, authenticity, or admissibility in evidence of any such interrogatory or response, or to any documents or information produced in response to a particular interrogatory. All objections to the use, at trial or otherwise, of any information or documents provided in response to these interrogatories are hereby expressly reserved.

4. Mylan objects to each interrogatory, definition, or instruction as overly broad, unduly burdensome, oppressive, and seeking information not relevant to any party's claim or defense nor proportional to the needs of the case (in accordance with Fed. R. Civ. P. 26(b)(1)) to the extent that it seeks or purports to seek information relating to information other than the subject matter of ANDA No. 207012 and will not produce such information.

5. Mylan objects to each interrogatory, definition, or instruction to the extent that it prematurely seeks production of information to be provided during expert discovery. Mylan will not prematurely respond with information that is to be provided during expert discovery, but will only respond in accordance with the Court's schedule for expert discovery. Mylan is available to meet and confer with Plaintiffs to determine an appropriate discovery schedule for the provision of information, documents, and things in accordance with the Scheduling Order, Local Rules for the District of Delaware, the Default Standard for Discovery Including Discovery of ESI, and the Federal Rules of Civil Procedure.

6. Mylan objects to each interrogatory to the extent that it seeks information, documents, or things containing private, confidential, secret, trade secret, proprietary, and/or sensitive business information of Mylan, its employees, and/or third parties ("Confidential Information"). Mylan will not produce Confidential Information to the extent that Mylan is under any obligation—whether imposed by a third party, court, tribunal, legislature, or any other body with authority to impose or enforce such an agreement, or by any statute, regulation,

or order—to maintain it in confidence and not disclose it, and all of Mylan responses should be read to exclude the production of such information. In addition, Mylan will not produce Confidential Information, and will redact Confidential Information from documents and information that it produces, to the extent that such Confidential Information is not relevant to any claim or defense in this action nor reasonably calculated to lead to the discovery of admissible evidence. The Confidential Information that Mylan will withhold and/or redact includes, but is not limited to, Confidential Information pertaining to individual patients involved in clinical trials; clinical trial investigators' personal information; the personal information of Mylan's employees; the configuration of Mylan's information technology systems; Mylan drugs not investigated or developed as part of the development of sorafenib; drugs belonging to other companies that have not received FDA approval; sales and budget forecasts; materials concerning the negotiation of agreements with third parties. All of Mylan's responses should be read to exclude the production of such information. Mylan will only produce other Confidential Information pursuant to the Protective Order in this action.

7. Mylan's responses herein are based on facts presently known to Mylan and represent a diligent and good faith effort to respond to the interrogatories. Mylan's discovery and investigation into the matters specified is continuing. Accordingly, Mylan reserves the right to supplement, alter or change its responses and objections to these interrogatories and to produce additional responsive information or documents, if any, that Mylan has in its possession, custody, or control at the time the interrogatories were propounded. Furthermore, Mylan reserves the right, at trial or during other proceedings in this action, to rely on documents, evidence, and other matters in addition to the documents or information produced in response to the interrogatories, whether or not such documents, evidence, or other matters are newly discovered or are now in existence but have not been identified or produced despite diligent and good faith efforts.

8. Mylan objects to each interrogatory, definition, or instruction to the extent that it seeks production of documents and electronically stored information from countries other than

the United States relating to ANDA No. 207012, on the grounds that such interrogatories are overly broad, unduly burdensome, and seek information not relevant to any party's claim or defense nor proportional to the needs of the case (in accordance with Fed. R. Civ. P. 26(b)(1)). Mylan will not produce such information, and Mylan's responses should be read to exclude the production of such documents and electronically stored information.

9. Mylan objects to each interrogatory, definition, or instruction to the extent it calls for the production of draft articles, submissions, publications or other documents, on the ground and to the extent that production of drafts of documents is unduly burdensome and not relevant to any party's claim or defense nor proportional to the needs of the case (in accordance with Fed. R. Civ. P. 26(b)(1)).

10. Mylan objects to each Interrogatory on the ground it seeks information concerning, and the disclosure of, proprietary and highly confidential information. If and to the extent Mylan agrees to provide any information, it will do so only subject to the protections of the protective order and/or a mutually acceptable supplemental protective order to address Mylan's confidentiality concerns.

11. Mylan objects to each Interrogatory to the extent it seeks information that is already in Plaintiffs' possession, custody, or control, or that are as readily available to Plaintiffs as they are to Mylan.

12. Mylan objects to each Interrogatory to the extent it seeks information whose disclosure is governed by Mylan's agreements with third parties, including confidentiality agreements. Mylan will provide such information only after complying with, and in compliance with, the terms of such third-party agreements.

13. Mylan objects to each Interrogatory to the extent it seeks information disclosure of which is governed by a protective order entered by a Court. Mylan will provide such information only after complying with, and in compliance with, the terms of the protective order.

14. Mylan objects to each Interrogatory, alone or in conjunction with the Definitions and Instructions that purports to impose obligations not imposed or contemplated by the Federal Rules of Civil Procedure, the Local Rules of the District of Delaware, or any agreements or stipulations entered into by the parties.

15. Mylan objects to each Interrogatory to the extent it assumes a disputed fact or legal conclusion in defining the information requested. Mylan denies any such disputed facts or legal conclusions assumed by such Interrogatory, and any response or objection to any Interrogatory is without prejudice to this objection.

16. Mylan objects to each Interrogatory to the extent it seeks information dated or prepared on or after January 30, 2015, the date of commencement of this litigation.

17. Mylan objects to each interrogatory to the extent it is directed at multiple issues and/or multiple parties, and thus constitutes multiple interrogatories under the guise of a single interrogatory. By responding to the interrogatories, Mylan in no way waives its right to object to the number of interrogatories, including subparts, which Plaintiffs have propounded or will propound in this action.

OBJECTIONS TO DEFINITIONS AND INSTRUCTIONS

18. Mylan objects to the definition of “Mylan’s ANDA Product” to the extent such term is overbroad and includes information that is not related to any claim or defense in this action, and is not reasonably calculated to lead to the discovery or admissible evidence and/or includes information outside of Mylan’s possession, custody, or control.

19. Mylan objects to the definition of “document” to the extent such term is overbroad and imposes discovery obligations broader than those imposed by the Federal Rules of Civil Procedure, the Local Rules for the District of Delaware, any Court orders, or any agreements or stipulations entered into by the parties. Mylan will comply with Plaintiffs’ Interrogatories pursuant to its obligations under Federal Rules of Civil Procedure, the Local Rules for the District of Delaware, the Court’s Scheduling Order entered in this case (Dkt. 33), or any agreements or stipulations entered into by the parties.

20. Mylan objects to Plaintiffs' definition of "you," "your," "yours," and "Mylan" as overly broad to the extent that it refers to the officers, directors, employees, divisions, parent companies, subsidiaries, affiliates, predecessors, or successors-in-interest, and any joint venture associated with Defendants, etc. Documents and electronically stored information in the possession, custody, or control of Mylan's officers, directors, employees, divisions, parent companies, subsidiaries, affiliates, predecessors, or successors-in-interest, and any joint venture associated with Defendants, etc., are not necessarily in the possession, custody, or control of Mylan, and Mylan will not construe the interrogatories to require production of such documents or electronically stored information to the extent that they are not in the possession, custody, or control of Mylan. Mylan responds on behalf of Mylan alone.

21. Mylan objects to each interrogatory, definition, and instruction to the extent that it seeks identification of "any" or "all" documents, information, communications, locations, persons, or corporations or other entities responsive to the interrogatory. Such demands are unduly burdensome and overly broad, and they seek documents and information that are not relevant to the claim or defense of any party nor proportional to the needs of the case, considering the importance of the issues at stake in the action, the amount in controversy, the parties' relative access to relevant information, the parties' resources, the importance of the discovery in resolving the issues, and whether the burden or expense of the proposed discovery outweighs its likely benefit. Indeed, many of Bayer's interrogatories are exceedingly broad—and constitute multiple interrogatories written in the form of a single interrogatory—and it would be extremely burdensome to respond to them. Mylan will use reasonable diligence to respond to Bayer's interrogatories based on information and/or documents in its possession, custody, or control, including based on a reasonable search of those files that are reasonably accessible and in which such information or documents ordinarily would be found and of files of those individuals whom Mylan reasonably believes are most likely to have responsive documents and/or information about the specific matters at issue. Where Mylan indicates that it will produce documents in response to an interrogatory, it means that it will produce only

those non-privileged responsive documents that it was able to identify and locate after such a reasonable search, if any, as set forth above. Mylan construes the interrogatories only to require the production of such responsive documents or information.

22. Mylan objects to the definition of “identify” insofar as this term requests that Mylan in that it requires Mylan, with respect to documents, to identify the “type of document,” “general subject matter,” “date of the document,” “author(s),” “addressee(s),” and “recipient(s).” The burden is the same for Bayer to discern this information upon review of the documents as it would be for Mylan. Mylan objects insofar as the definition imposes discovery obligations broader than those imposed by the Federal Rules of Civil Procedure, the Local Rules for the District of Delaware, any Court orders, or any agreements or stipulations entered into by the parties. Mylan will comply with Plaintiffs’ Interrogatories pursuant to its obligations under Federal Rules of Civil Procedure, the Local Rules for the District of Delaware, the Court’s Scheduling Order entered in this case (Dkt. 33), or any agreements or stipulations entered into by the parties.

23. Mylan objects to Instruction No. 7 insofar as it imposes discovery obligations broader than those imposed by the Federal Rules of Civil Procedure, the Local Rules for the District of Delaware, any Court orders, or any agreements or stipulations entered into by the parties. Mylan will provide a privilege log pursuant to the parties’ Stipulation and Order on E-Discovery, or any other agreements or stipulations entered into by the parties.

SPECIFIC OBJECTIONS AND RESPONSES

INTERROGATORY NO. 1:

Do you contend that the manufacture, use, sale, offer for sale, or importation of Mylan’s ANDA Product, including use of Mylan’s ANDA Product in accordance with the proposed labeling (including the prescribing information and patient package insert) for such product, would not infringe one or more claims of the patents-in-suit, assuming the claims to be valid and enforceable? If your answer is that one or more of these claims would not be infringed, identify the claims that you contend would not be infringed, state all bases on which you

contend any such claim would not be infringed either literally or under the doctrine of equivalents, including any basis upon which you assert that Plaintiffs are estopped from asserting infringement by the doctrine of equivalents, state all facts on which you rely for your contentions, and identify all documents and circumstances relating to those facts and all individuals with knowledge of those facts.

RESPONSE TO INTERROGATORY NO. 1:

Mylan incorporates the General Objections set forth above. Mylan objects to this interrogatory as overly broad, unduly burdensome, and oppressive to the extent it seeks information that is irrelevant to the claims and defenses at issue in this case and is not proportional to the needs of the case. For example, Mylan objects to the phrase “all bases,” “any basis,” “all facts,” “all documents and circumstances,” and “all individuals” as being overly broad and requiring the production of trivial documents and other documents with limited, if any, relevance to the parties’ claims or defenses. Mylan further objects to the phrases “one or more claims” and “any such claim” to the extent that this interrogatory seeks information not relevant to the asserted claims. Mylan will be responding to this interrogatory only insofar as it is relevant to the claims currently asserted by Plaintiffs. Mylan objects to this Interrogatory to the extent it calls for a legal conclusion. Mylan further objects to this interrogatory as premature under the Scheduling Order, as discovery is just beginning, Mylan has not received any discovery from Bayer, and no depositions have been conducted. Mylan further objects to this interrogatory to the extent that Mylan does not bear the burden of proof regarding infringement. Mylan further objects to this interrogatory as premature under the Local Rules and the Default Standard for Discovery Including Discovery of ESI, which requires Plaintiffs to produce initial claim charts demonstrating how each product allegedly infringes each asserted patent claim before Defendants provide any initial contentions. This interrogatory essentially requires Mylan to provide non-infringement contentions before Plaintiffs have provided its infringement contentions. Mylan further objects to this interrogatory as seeking expert discovery prior to the dates for expert reports. Mylan objects to

this interrogatory to the extent it seeks information that is confidential, protected by the right of privacy, and/or protected from disclosure by applicable privileges and protections, including without limitation the attorney-client privilege, work product protection, common interest privilege and/or consulting expert privilege. Mylan objects to this interrogatory to the extent it seeks information the disclosure of which is subject to third-party confidentiality obligations or a protective order. Mylan objects to this interrogatory to the extent it requests information not in Mylan's possession, custody, or control. Mylan objects to this interrogatory to the extent it calls for information already in Plaintiffs' possession, or calls for publicly available information. Mylan objects to this interrogatory as vague and ambiguous as to the terms "proposed labeling" and "circumstances." Mylan proposes that the parties meet and confer to determine a meaning. Mylan objects to this interrogatory to the extent it includes multiple subparts, each of which constitutes a separate Interrogatory pursuant to Fed. R. Civ. P. 33(a)(1). Mylan further objects to this interrogatory as improper under Fed. R. Civ. P. 33(a) because it purports to be a single interrogatory but contains multiple subparts. This interrogatory has at least five discrete subparts and is, therefore, at least five interrogatories. Mylan further objects to the description of this interrogatory as Interrogatory No. 1. Mylan considers this interrogatory to be Interrogatory Nos. 1-5.

Subject to and without waiving the foregoing objections, and to the extent understood, Mylan responds that it is Plaintiffs' burden to provide initial infringement contentions under the Scheduling Order. Mylan will supplement its response after Plaintiffs provide appropriate infringement contentions.

Discovery is on-going and Mylan will supplement its response if necessary and in accordance with the Federal Rules of Civil Procedure. Mylan is available to meet and confer with Plaintiffs to determine an appropriate discovery schedule for the provision of information, documents, and things in accordance with the Scheduling Order, Local Rules for the District of Delaware, the Default Standard for Discovery Including Discovery of ESI, and the Federal Rules of Civil Procedure.

INTERROGATORY NO. 2:

Assuming that the use of Mylan's ANDA Product, including the use of such product in accordance with the proposed labeling (including the prescribing information and patient package insert) for such product, is determined to infringe each claim of the patents-in-suit and that each claim is determined to be valid and enforceable, do you contend that the manufacture, sale, offer for sale, or importation of Mylan's ANDA Product would not induce the infringement of one or more claims of the patents-in-suit? If your answer is that none of these actions would induce infringement, identify the claims you contend would not be infringed, all bases on which you contend any such claims would not be infringed, and all facts on which you rely for your contentions.

RESPONSE TO INRESPONSE TO INTERROGATORY NO. 2:

Mylan incorporates the General Objections set forth above. Mylan objects to this interrogatory as overly broad, unduly burdensome, and oppressive to the extent it seeks information that is irrelevant to the claims and defenses at issue in this case and is not proportional to the needs of the case. For example, Mylan objects to the phrase "all bases" and "all facts" as being overly broad and requiring the production of trivial documents and other documents with limited, if any, relevance to the parties' claims or defenses. Mylan further objects to the phrases "each claim of the patents-in-suit," "any such claims," and "one or more claims" to the extent that this interrogatory seeks information not relevant to the asserted claims. Mylan will be responding to this interrogatory only insofar as it is relevant to the claims currently asserted by Plaintiffs. Mylan objects to this interrogatory to the extent it calls for a legal conclusion. Mylan further objects to this interrogatory as premature under the Scheduling Order, as discovery is just beginning, Mylan has not received any discovery from Bayer, and no depositions have been conducted. Mylan further objects to this interrogatory as premature to the extent that Bayer has not established that Mylan's ANDA product would infringe each claim of the patents-in-suit, nor has there been any finding that each claim is valid and enforceable. Mylan further objects to this interrogatory to the extent that Mylan does not

bear the burden of proof regarding infringement, including induced infringement. Mylan further objects to this interrogatory as premature under the Local Rules and the Default Standard for Discovery Including Discovery of ESI, which requires Plaintiffs to produce initial claim charts demonstrating how each product allegedly infringes each asserted patent claim before Defendants provide any initial contentions. This interrogatory essentially requires Mylan to provide non-infringement contentions before Plaintiffs have provided its infringement contentions. Mylan further objects to this interrogatory as seeking expert discovery prior to the dates for expert reports. Mylan objects to this interrogatory to the extent it seeks information that is confidential, protected by the right of privacy, and/or protected from disclosure by applicable privileges and protections, including without limitation the attorney-client privilege, work product protection, common interest privilege and/or consulting expert privilege. Mylan objects to this interrogatory to the extent it seeks information the disclosure of which is subject to third-party confidentiality obligations or a protective order. Mylan objects to this interrogatory to the extent it requests information not in Mylan's possession, custody, or control. Mylan objects to this interrogatory to the extent it calls for information already in Plaintiffs' possession, or calls for publicly available information. Mylan further objects to this interrogatory as improper under Fed. R. Civ. P. 33(a) because it purports to be a single interrogatory but contains multiple subparts. This interrogatory has at least three discrete subparts and is, therefore, at least three interrogatories. Mylan further objects to the description of this interrogatory as Interrogatory No. 2. Mylan considers this interrogatory to be Interrogatory Nos. 6-8.

Subject to and without waiving the foregoing objections, Mylan responds that it is Plaintiffs' burden to provide initial infringement contentions under the Scheduling Order. Mylan will supplement its response after Plaintiffs provide appropriate infringement contentions.

Discovery is on-going and Mylan will supplement its response if necessary and in accordance with the Federal Rules of Civil Procedure. Mylan is available to meet and confer

with Plaintiffs to determine an appropriate discovery schedule for the provision of information, documents, and things in accordance with the Scheduling Order, Local Rules for the District of Delaware, the Default Standard for Discovery Including Discovery of ESI, and the Federal Rules of Civil Procedure.

INTERROGATORY NO. 3:

Do you contend that any of the claims of the patents-in-suit are invalid? If your answer is anything other than an unequivocal “no,” state all bases for your contention and identify for each challenged claim all facts, documents, and circumstances on which you rely for your contention, including but not limited to an identification of the portion(s) of any statutes or legal doctrines under which you contend such claim is invalid and all bases for each such contention; the identification of any prior art or other references or information which you contend renders such claim invalid (either alone or in combination with other references or information); the identification, for each reference on which you rely, of what limitations of such claim are and are not disclosed by each reference and the portion(s) of each reference on which you rely for each limitation of the claim; and, to the extent you have an obviousness contention, the identification of the reference(s) that you contend should be modified or combined and all bases for your contention that there is a reason to modify the reference(s) and that there would have been a reasonable expectation of success.

RESPONSE TO INTERROGATORY NO. 3:

Mylan incorporates the General Objections set forth above. Mylan objects to this interrogatory as overly broad, unduly burdensome, and oppressive to the extent it seeks information that is irrelevant to the claims and defenses at issue in this case and is not proportional to the needs of the case. For example, Mylan objects to the phrase “all bases,” “all facts, documents, and circumstances,” and “any prior art or other references or information,” as being overly broad and requiring the production of trivial documents and other documents with limited, if any, relevance to the parties’ claims or defenses. Mylan further objects to the phrase “any of the claims” to the extent that this interrogatory seeks information not relevant to the

asserted claims. Mylan will be responding to this interrogatory only insofar as it is relevant to the claims currently asserted by Plaintiffs. Mylan objects to this interrogatory to the extent it calls for a legal conclusion. Mylan further objects to this interrogatory as premature under the Scheduling Order, as discovery is just beginning, Mylan has not received any discovery from Bayer, and no depositions have been conducted. Mylan further objects to this interrogatory as premature under the Local Rules and the Default Standard for Discovery Including Discovery of ESI, which requires Plaintiffs to produce initial claim charts demonstrating how each product allegedly infringes each asserted patent claim before Defendants provide any initial contentions. Mylan further objects to this interrogatory as seeking expert discovery prior to the dates for expert reports. Mylan objects to this interrogatory to the extent it seeks information that is confidential, protected by the right of privacy, and/or protected from disclosure by applicable privileges and protections, including without limitation the attorney-client privilege, work product protection, common interest privilege and/or consulting expert privilege. Mylan objects to this interrogatory to the extent it seeks information the disclosure of which is subject to third-party confidentiality obligations or a protective order. Mylan objects to this interrogatory to the extent it requests information not in Mylan's possession, custody, or control. Mylan objects to this interrogatory to the extent it calls for information already in Plaintiffs' possession, or calls for publicly available information. Mylan objects to this interrogatory as vague and ambiguous as to the phrases "portion(s)," "modified," "circumstances." Mylan proposes that the parties meet and confer to determine a meaning. Mylan objects to this interrogatory to the extent it includes multiple subparts, each of which constitutes a separate Interrogatory pursuant to Fed. R. Civ. P. 33(a)(1). Mylan further objects to this interrogatory as improper under Fed. R. Civ. P. 33(a) because it purports to be a single interrogatory but contains multiple subparts. This interrogatory has at least six discrete subparts and is, therefore, at least six interrogatories. Mylan further objects to the description of this interrogatory as Interrogatory No. 3. Mylan considers this interrogatory to be Interrogatory Nos. 9-14.

Subject to and without waiving the foregoing objections, and to the extent understood, Mylan responds that the answer to this interrogatory may be derived from Mylan's Notice Letters of November 9, 2015 and December 19, 2014, both of which are incorporated by reference herein. In addition to Mylan's Notice Letters of November 9, 2015 and December 19, 2014, Mylan further responds as follows: Claims 7-9 of the '141 patent claim a method of treating "a tumor of the kidney." However, there are no examples, data or other information that would permit a person to practice the full scope of this claim without undue experimentation. Therefore, these claims are invalid for lack of enablement and written description under § 112(a).

Claim 35 of the '834 patent is directed to "[a] compound of Formula I: A—D—B or a pharmaceutically acceptable salt thereof, wherein D is —NH—C(O)—NH—, A is a substituted moiety of the formula: —L—M—L¹..." Neither the claim, written description, nor prosecution history of the '834 patent defines the value of "M." Claims 36-38 depend from claim 35, and similarly fail to define the value of "M." A person of ordinary skill in the art would be unable to make or use the claimed compound without knowing the complete identity of the compound. The lack of disclosure of "M" also does not allow the public to understand what chemical entity the inventor(s) claim as their invention. *General Electric Co. v. Wabash Appliance Corporation*, 304 U.S. 364 (1938) ("The inventor must 'inform the public during the life of the patent of the limits of the monopoly asserted, so that it may be known which features may be safely used or manufactured without a license and which may not.'"). Therefore, at least claims 35-38 of the '834 patent are invalid for lack of enablement and written description under § 112(a).

Claims 35-38 are also invalid for being indefinite, as these claims fail to particularly point out and distinctly claim the subject matter which the inventor(s) regard as the invention under § 112(b). *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1562, 37 U.S.P.Q.2d 1618 (Fed. Cir. 1996) ("the language of the claims must make it clear what subject matter they encompass."); *Technology Innovations, LLC v. Amazon.com, Inc.*, 2014 WL

1292093, *3-*5 (D. Del. 2014). Discovery is on-going and Mylan will supplement its response if necessary and in accordance with the Federal Rules of Civil Procedure. Mylan is available to meet and confer with Plaintiffs to determine an appropriate discovery schedule for the provision of information, documents, and things in accordance with the Scheduling Order, Local Rules for the District of Delaware, the Default Standard for Discovery Including Discovery of ESI, and the Federal Rules of Civil Procedure.

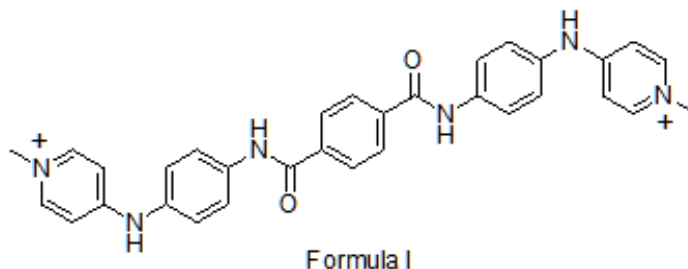
SUPPLEMENTARY RESPONSE INTERROGATORY NO. 4:

Mylan incorporates by reference the General Objections, Objections to Definitions and Instructions, and each specific objection set forth above as if fully stated herein. Mylan supplements its response to Interrogatory No. 3 as follows:

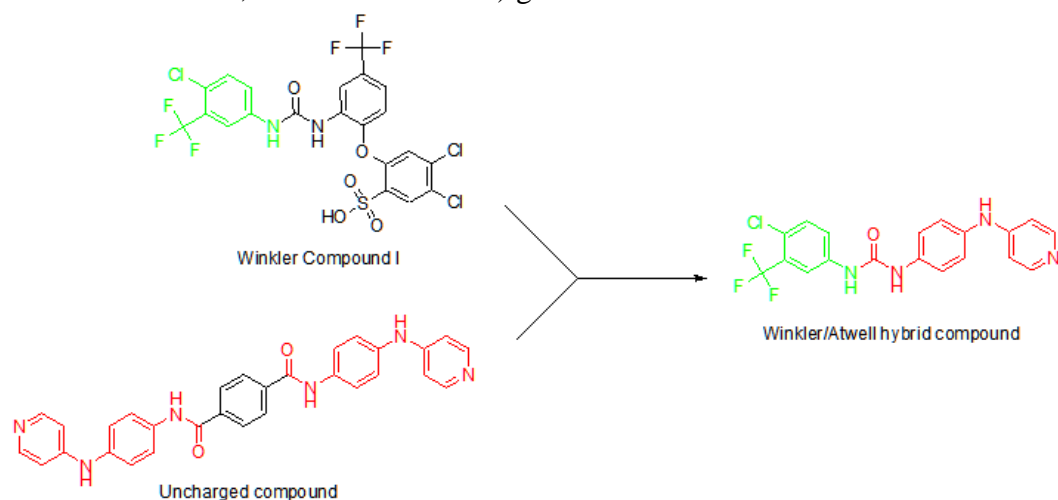
I. U.S. PATENT NOS. 7,235,576, 7,351,834, AND 7,897,623

Plaintiffs have asserted claims 1-17 of the '576 patent, claims 1-8 of the '623 patent, and claims 39-41 of the '834 patent. The elements of these claims are described in the November 9, 2015 Notice Letter, which is incorporated by reference herein and also attached as Ex. B. *See* November 9, 2015 Notice Letter at 14-44. In addition to the noninfringement and invalidity defenses described in the November 9, 2015 Notice Letter, each of these claims are also rendered invalid for obviousness by Atwell *et al.*, Journal of Medicinal Chemistry (1968), 11(4), 690-4 ("Atwell"), in view of Winkler, in view of either Tang or Haga, and in further view of known solubility concerns.

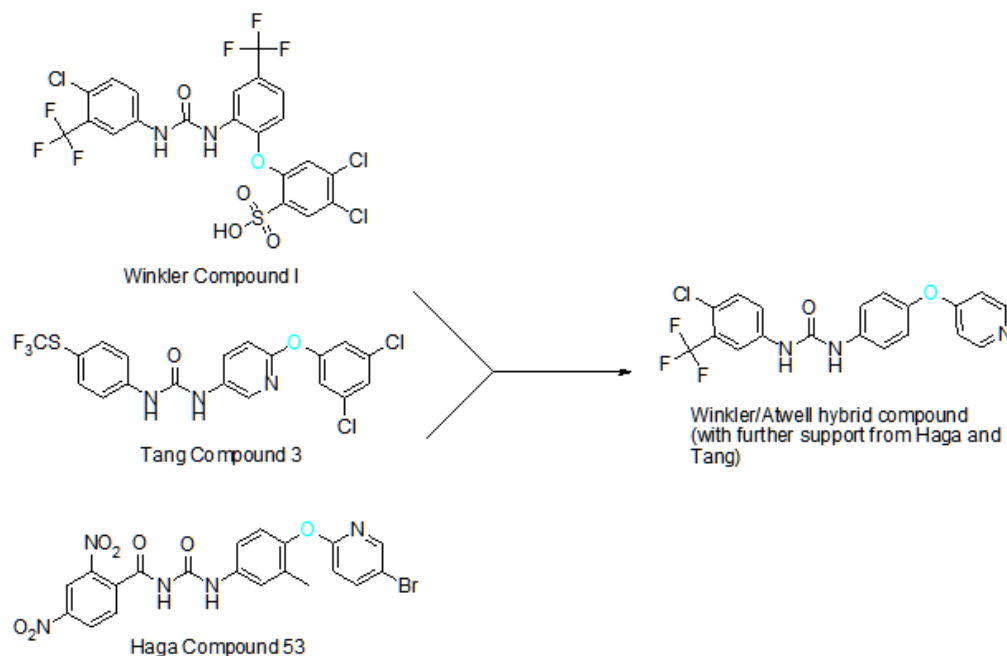
Atwell describes anti-tumor compounds of Formula (I):



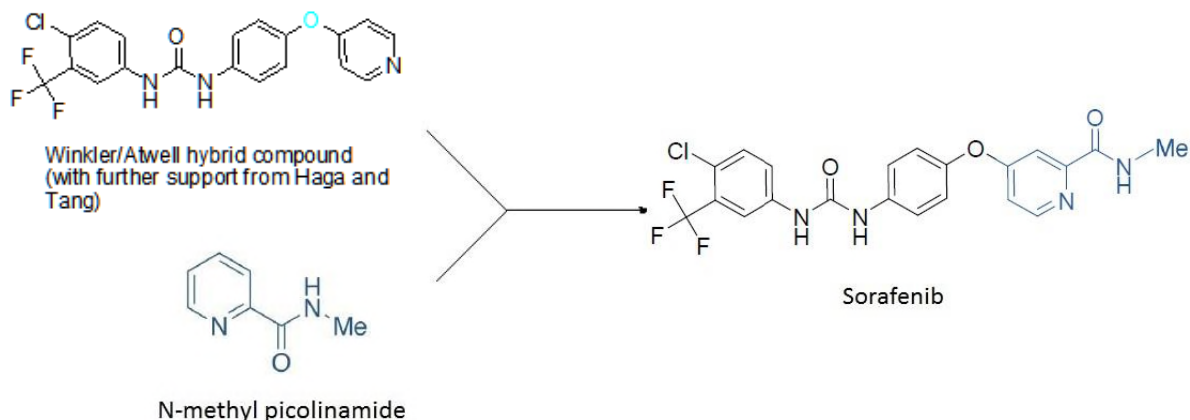
A POSITA would understand that the relatively poor absorption of quaternary ammonium compounds from the lumen of the gastrointestinal tract limits their utility in therapy. *See, e.g.* U.S. Patent No. 2,899,357, col. 1, ll. 20-50. Thus, the “uncharged compound” would be the obvious lead compound. Highlighted in red is the amine portion of the molecule that when combined with Compound I taught in Winkler (also described in detail in the November 9, 2015 Notice Letter) gives:



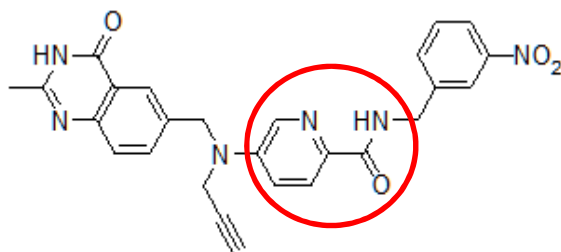
Furthermore, Winkler, Tang, and Haga, as described in the November 9, 2015 Notice Letter, teach preferred antitumor compounds with an ether linkage between the aryl/heteroaryl groups. Thus, a POSA in the art would be motivated to replace the amino linker with oxygen.



As further described in the November 9, 2015 Notice Letter, it was also known since at least September 5, 1989, that diphenyl ureas have poor solubility. Haga at col. 26, ll. 3-4, Compound 53. It was further known that nicotinamide and picolinamide have high solubility in water. N-methyl picolinamide, an obvious derivative of picolinamide, would be an obvious adduct to the Winkler/Atwell hybrid compound, which could be used by one of ordinary skill in the art to enhance the solubility of a anti-cancer drug while maintaining its potency and improving binding in an enzyme receptor pocket. Accordingly, incorporating N-methylpicolinamide into the Winkler/Atwell hybrid compound would enhance its solubility resulting in better bioavailability and also enhanced binding to the enzyme receptor pocket. The enhanced solubility provided by incorporating N-methylpicolinamide would result in the sorafenib structure. The resulting sorafenib structure, which has the N-methyl picolinamide shown in blue, is illustrated below:

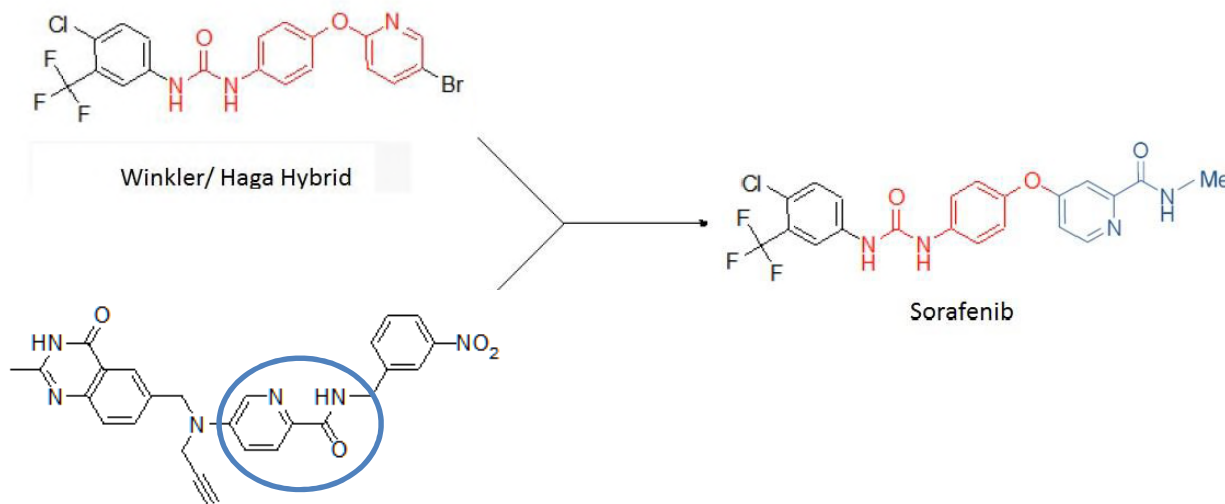


The pyridine-2-carboxamide substructure present in sorafenib is also disclosed in prior art relating to other pharmaceutical agents. U.S. Patent No. 5,252,573 (“the ’573 patent”), filed on November 18, 1991, and issued on October 12, 1993, relates to quinazoline derivatives, or pharmaceutically acceptable salts thereof, which possess anti-tumor activity, their manufacture, and pharmaceutical compositions containing them. ’573 patent at col. 21, ll. 26-68. Example 4 of the ’573 patent discloses 5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)pyridine-2-carboxamide (Example 4, col. 31, ll. 5 – 39), as a preferred compound (col. 9, l. 32) and specifically claims this compound (Claim 5):



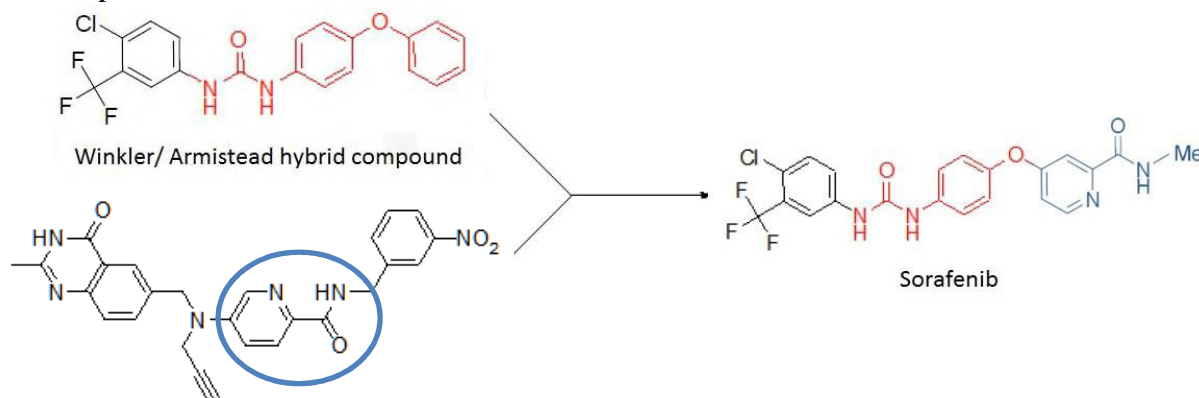
Therefore, the ’573 patent, which relates to compounds known to possess anti-tumor activities, and which presents Example 4 as a preferred compound, would render obvious 1-17 of the ’576 patent, claims 1-8 of the ’623 patent, and claims 39-41 of the ’834 patent, by motivating a POSA to incorporate the pyridine-2-carboximide substructure with the lead compounds described previously.

For example, the Winkler/Haga hybrid compound (*see* November 9, 2015 Notice Letter at 74-75) in view of the preferred compound disclosed as Example 4 in the '573 patent renders obvious 1-17 of the '576 patent, claims 1-8 of the '623 patent, and claims 39-41 of the '834 patent:



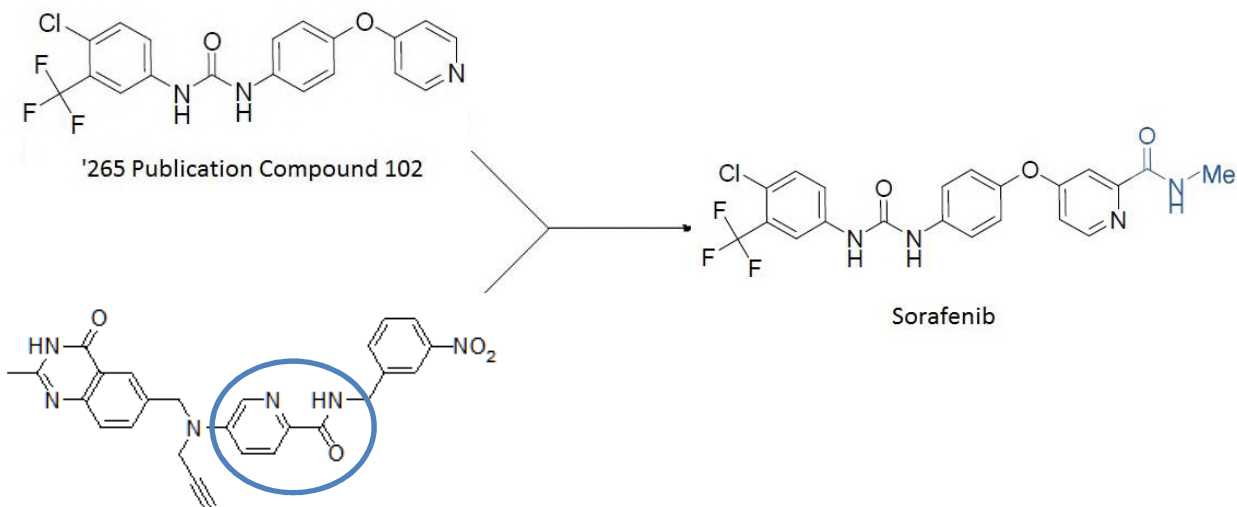
'573 patent at Example 4, col. 31, ll. 5 – 39

Similarly, the Winkler/Armistead hybrid compound (*see* November 9, 2015 Notice Letter at 76-77) in view of the preferred compound disclosed as Example 4 in the '573 patent renders obvious 1-17 of the '576 patent, claims 1-8 of the '623 patent, and claims 39-41 of the '834 patent:



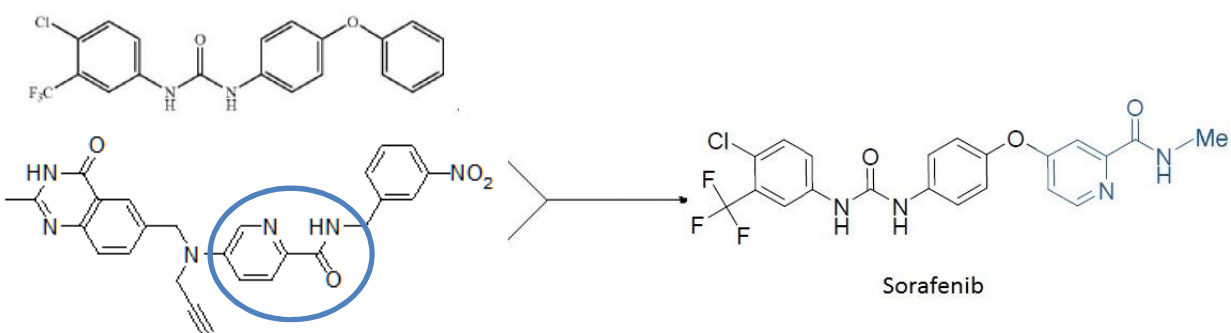
Similarly, Compound 102, as disclosed in the '265 publication (*see* November 9, 2015 Notice Letter at 78-79) in view of the preferred compound disclosed as Example 4 in the '573

patent renders obvious 1-17 of the '576 patent, claims 1-8 of the '623 patent, and claims 39-41 of the '834 patent:



'573 patent at Example 4, col. 31, ll. 5 – 39

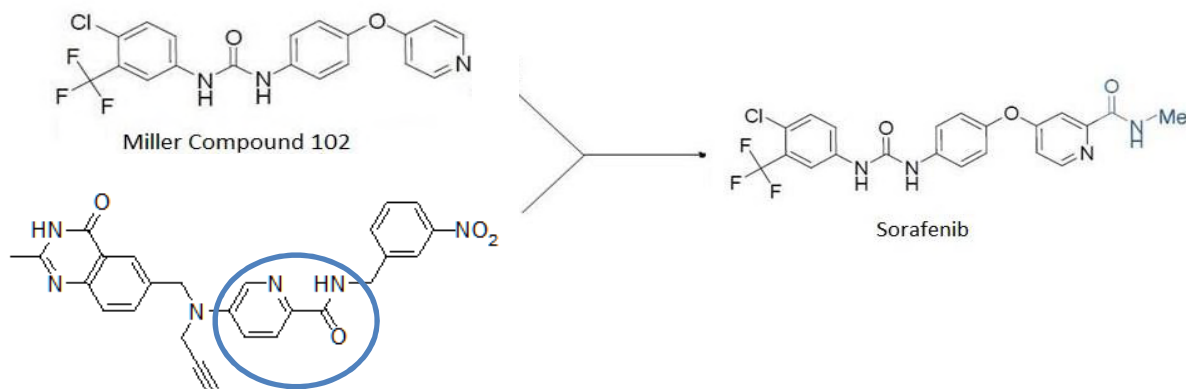
Similarly, Compound 166, as disclosed in the '880 patent (*see* November 9, 2015 Notice Letter at 80-81) in view of the preferred compound disclosed as Example 4 in the '573 patent renders obvious 1-17 of the '576 patent, claims 1-8 of the '623 patent, and claims 39-41 of the '834 patent:



'573 patent at Example 4, col. 31, ll. 5 – 39

A POSA would consider it obvious to modify Compound 102 as disclosed in Miller PCT to incorporate the pyridine-2-carboximide substructure in light of the disclosure of Compound 101, as disclosed in Dumas. *See* November 9, 2015 Notice Letter at 95-97.

Example 4 of in the '573 patent provides further support to add this substructure and to render claims 1-17 of the '576 patent obvious:



'573 patent at Example 4, col. 31, ll. 5 – 39

II. U.S. PATENT NO. 8,841,330

The elements of claims 4, 10, 13, and 14 of the '330 patent (“the '330 asserted claims”) are described in the November 9, 2015 Notice Letter. *Id.* at 46-48. Each of the '330 asserted claims claim sorafenib or its tosylate salt. Thus, this element of each of the '330 asserted claims is not novel or is obvious. Accordingly, Defendants incorporate by reference the arguments set forth above for the '576 patent, the '834 patent, and the '623 patent. Additionally, as described in the November 9, 2015 Notice Letter, claims 4, 10, 13, and 14 are invalid under § 112 for lacking adequate written description and enablement. November 9, 2015 Notice Letter at 111-15. Each of these claims is also rendered invalid for obviousness by the '265 publication and/or Dumas alone or in combination with one another.

The '265 publication was published on October 30, 2008, from U.S. Application Serial No. 12/145,679 as a continuation of application Serial No. 09/776,936 filed on December 22, 1998. The '265 publication describes symmetrical and unsymmetrical substituted diphenyl ureas useful for the treatment of a cancerous cell growth mediated by raf kinase. As discussed

above, the prior art renders the sorafenib compound obvious. Additionally, the '265 publication teaches that the use of such compounds are "useful in pharmaceutical compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase." '265 Publication at [0003]. Additionally, it explicitly states that the "compounds of the invention are useful in treating solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder, or colon" *Id.* The '265 publication additionally discloses a "method for the treatment of a cancerous cell growth." *Id.* at [0020]. It also discloses that the "daily oral dosage regimen will be preferably be from 0.01 to 200 mg/kg of total body weight, thereby discloses the "effective amount" of claims 1 and 13. *Id.* at [0069]. Further the '265 publication provides various "administration" techniques along with the recommended dose. *Id.*

Published on July 1, 1999, and having an international filing date of December 22, 1998, Dumas claims priority to U.S. Application Serial No. 08/996,343 filed on December 22, 1997. Dumas discloses "[m]ethods of treating tumors mediated by raf kinase, with substituted urea compounds." Dumas at Abstract. In particular, it teaches that such compounds are "useful in treating solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon)." Dumas at 2:11-14. Like the '265 Publication, Dumas also provides methods for administering and preferred dosage amounts. *Id.* at 27:20-30.

Each and every claim limitation of the '330 patent is met by both Dumas and the '265 Publication as discussed above. Thus, asserted claims 4, 10, 13, and 14 of the '330 patent are invalid as obvious over the '265 publication or Dumas alone or in combination with one another.

III. U.S. PATENT NO. 8,618,141

Plaintiffs have asserted claims 7-9 and 11 of the '141 patent. The elements of those claims are described in the December 19 2014 Notice Letter ("the '141 Notice Letter"), incorporated by reference herein and also attached as Ex. A. '141 Notice Letter at 11, 21, 23. Each of these claims are invalid as anticipated by '012 Publication under 35 U.S.C. § 102(b). The preamble of claim 7 of the '141 patent should not be construed as a limitation; however, even if it is, the claim would nevertheless be anticipated. The preamble states "a method of blocking tumor angiogenesis in a human or other mammal" Claim 7. Sorafenib's biochemical property of blocking tumor angiogenesis through KDR (VEGFR-2) inhibition as disclosed in the '141 patent is an inherent property. Thus, sorafenib would "block tumor angiogenesis" every time that sorafenib is used to treat a tumor in a patient.

By the time of the filing of the application that lead to the '141 patent, the method of treating patients with tumors by administration of sorafenib tosylate was known. It was also known that tumor angiogenesis was a "prerequisite" for the substantive growth of tumors. *See* '141 patent, 2:1-2. The '141 patent discloses that sorafenib inhibits KDR (VEGFR-2). Inhibition of KDR (VEGFR-2) blocks angiogenesis. John K. Buolamwini, "Novel Anticancer Drug Discovery," *Curr. Opin. Chem. Biol.* Aug. 1999, 3(4):500-09 ("Buolamwini") at 502, 505-06. Thus, the prior art method of administering sorafenib tosylate to patients with tumors necessarily blocked tumor angiogenesis by inhibiting KDR (VEGFR-2).

Here, the method disclosed by the prior art was the administration of sorafenib to patients having solid tumors. The "natural and inherent results" of that method are the inhibition of tumor growth by inhibition of Raf kinase (recognized result) and the inhibition of angiogenesis by the inhibition of KDR (VEGFR-2) activity (unrecognized result). The '141

patent claims the exact method disclosed in PCT Publication No. WO 00/42012 to Riedl et al. (“the ‘012 publication”), which was published on July 20, 2000 and is thus 102(b) prior art to the ‘141 patent; the administration of sorafenib to patients results in the particular benefits of Raf inhibition and KDR inhibition. *See Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368, 1378 (Fed. Cir. 2005) (for a reference to anticipate a method claim inherently, the prior art must first “disclose[] the very same methods, then the particular benefits must naturally flow from those methods even if it is not recognized at the time . . .”). Thus, claims 8 and 9 are anticipated regardless of whether the preamble is considered to be a limitation of the claims.

Furthermore, the ‘012 publication specifically discloses the pharmaceutical composition to have a “daily oral dosage regimen” to “preferably be from 0.01 to 200 mg/Kg of total body weight.” ‘012 publication at 12:31-32. Thus, claim 11 is expressly anticipated by the ‘012 publication.

For at least these reasons, claims 7-9 and 11 of the ‘141 patent are invalid as anticipated by the ‘012 publication under 35 U.S.C. § 102(b).

Claim 7 of the ‘141 patent is invalid either as anticipated under 35 U.S.C. § 102 over the ‘012 publication or as obvious under 35 U.S.C. § 103(a) over the ‘012 publication, in view of Rika Hoshino et al., “Constitutive activation of the 41-/43-kDa mitogen-activated protein kinase signaling pathway in human tumors,” *Oncogene* Jan. 21, 1999, 18:813-22 (“Hoshino”). As discussed above, the ‘012 publication discloses that sorafenib is useful in treating solid tumors, providing non-limiting examples of lung, pancreas, thyroid, bladder, and colon tumors. ‘012 publication at 2:18-20. Claim 7 of the ‘141 patent recites a method of blocking tumor angiogenesis in a tumor of the kidney comprising administering sorafenib. A person of ordinary skill in the art would recognize that a kidney tumor is a solid tumor and that the ‘012

publication's disclosure of the treatment of solid tumors would encompass the treatment of a kidney tumor. This would render claim 7 invalid as anticipated under 35 U.S.C. § 102(b), as articulated above.

Claims 7 and 11 are invalid as obvious under 35 U.S.C. § 103(a) over the '012 publication in view of Hoshino. From the '012 publication, one of skill in the art would know that sorafenib could be administered to patients having solid tumors and the effective amount to be administered, as detailed above and in the '141 Notice Letter. One of skill in the art would also know that sorafenib could be formulated as a tosylate salt for oral administration. Finally, the skilled artisan would know that sorafenib tosylate would act as a raf inhibitor to combat cancerous tumors. One of skill in the art, who would be an experienced scientist familiar with medicinal chemistry, biochemical pathways involved with cancer, and anti-cancer therapies, would recognize that sorafenib tosylate would be an effective treatment of any cancer in which Raf was implicated. Hoshino identifies kidney cancer as one such cancer. Hoshino at 815. Specifically, Hoshino shows that MAP kinases are overactive in human kidney tumors. *Id.* Hoshino also demonstrates that MEK and raf activation are responsible for that elevated MAP kinase activity. *Id.* at 815-16; Table 4. Knowing that sorafenib was an inhibitor of raf and effective in treating solid tumors from the '012 publication, it would be obvious for one of skill in the art to employ sorafenib in the treatment of kidney tumors (a type of solid tumor). Accordingly, claims 7 and 11 would be obvious under 35 U.S.C. § 103(a) to one of skill in the art over the '012 publication in view of Hoshino.

Claims 8 and 9 of the '141 patent are also obvious over the '012 publication in view of Buolamwini. Claim 8 depends on claim 7, and further states “wherein the tumor of the kidney that is treated is characterized by abnormal angiogenesis or hyperpermeability processes, which

are neither raf-mediated nor p38-mediated.” Claim 9 reads: “A method as in Claim 8 wherein the tumor of the kidney that is treated is characterized by abnormal angiogenesis or hyperpermeability processes, which are mediated by KDR (VEGFR-2).” As discussed above, the inhibition of abnormal angiogenesis mediated by KDR (VEGFR2) is a natural outcome of the administration of sorafenib disclosed by the ’012 publication.

One of skill in the art would know that sorafenib inhibited Raf kinase, and that its administration to patients would be an effective treatment for solid tumors. *See* discussion above. One of skill in the art would also know that Raf is activated with KDR (VEGFR-2)-mediated tumor angiogenesis. *See* Buolamwini at 501-504. Accordingly, it would be obvious for one of skill in the art to use sorafenib to inhibit KDR (VEGFR-2)-mediated angiogenesis by inhibiting Raf—an enzyme involved in VEGF’s angiogenic effects. Accordingly, claims 8 and 9 are invalid as obvious under 35 U.S.C. § 103(a) over the ’012 publication and Buolamwini.

For at least these reasons, claims 7-9 and 11 of the ’141 patent are invalid as obvious under 35 U.S.C. § 103(a) over the prior art. Mylan reserves the right to supplement these initial invalidity contentions to substitute other references to combine and/or to identify motivations to combine particular references with one another with additional particularity.

In addition, claims 7-9 and 11 of the ’141 patent are invalid in view of the doctrine of obviousness-type double patenting. The double patenting doctrine is designed to prevent “unjustified timewise extension of the right to exclude.” *In re Van Ornum*, 686 F.2d 937, 943-44 (C.C.P.A. 1982). For instance, the doctrine bars an applicant from obtaining separate patents with separate terms for both a product and process for making that product, unless the product and process are “patentably distinct.” *See In re Taylor*, 53 C.C.P.A. 1187, 360 F.2d 232, 234 (1966); *In re Cady*, 22 C.C.P.A. 1190, 77 F.2d 106, 109 (1935) (instructing that

“double patenting is not sustainable when the product can be fabricated by processes other than that secured by the issued process patent”) (quotation marks omitted).

Claims 7-9 and 11 of the '141 patent are invalid under the doctrine of obviousness-type double patenting over claims 1, 7, 13, and 14 of U.S. Patent No. 8,841,330 (“the '330 patent”). Claim 1 of the '330 patent recites a method for the treatment of a tumor of the prostate, breast, liver, ovary or cervix in a human or animal comprising administering an effective amount of sorafenib or a pharmaceutically acceptable salt thereof. Claim 7 of the '330 patent claims the same method as claim 1, but uses the tosylate salt of sorafenib. Claims 13 and 14 of the '330 patent are similar to the claims 1 and 7 respectively, except claims 13 and 14 are limited to the treatment of liver cancer. Claims 7-9 and 11 of the '141 patent are invalid under the doctrine of obviousness-type double patenting because the differences between the asserted claims in the '141 patent and the claims of the '330 patent are not patentably distinct. The '141 patent merely claims an inherent and/or obvious variant of the '330 claims—treating kidney tumors (claims 7, 8, 9 and 11) and merely restates the effective amount of sorafenib to be “0.01 to 200 mg/kg of total body weight” (claim 11), which is inherent and obvious in light of claims 1, 7, 13, and 14 of the '330 patent, which recite a method for administering sorafenib (or its tosylate salt) in an “effective amount.” Treating kidney tumors is inherent and/or an obvious variant of the '330 patent because as mentioned above, treating KDR-mediated tumors is a natural outcome of administering sorafenib in an “effective amount.” Thus, claims 7-9 and 11 of the '141 patent are invalid under the doctrine of obviousness-type double patenting over claims 1, 7, 13, and 14 of the '330 patent because the claims are not patentably distinct and only serve to extend the exclusive rights granted to Plaintiffs by the '330 patent.

Claims 7-9 and 11 are also invalid under the doctrine of obviousness-type double patenting in view of claims 1, 6, 8, and 13 of U.S. Patent No. 8,124,630 (“the ’630 patent”). Claim 1 of the ’630 patent recites a “method for treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon in a human or animal in need thereof comprising administering an effective amount of [sorafenib] . . . or a pharmaceutically acceptable salt thereof.” Claim 6 depends from claim 1 and claims a method for the treatment of carcinoma of the bladder in a human in need thereof. Claim 8 mirrors claim 1 using the tosylate salt of [sorafenib]. Claim 13 depends from claim 8 and claims a method for the treatment of carcinoma of the bladder. Similar to the analysis above with respect to the ’330 patent, claims 1, 6, 8, and 13 of the ’630 patent render the claims of the ’141 patent obvious. Thus, claims 7-9 and 11 of the ’141 patent are invalid under the doctrine of obviousness-type double patenting.

Claim 11 of the ’141 patent claims a method of blocking angiogenesis in “a tumor of the kidney.” As discussed in the Response to Interrogatory No. 3 above, there are no examples, data or other information that would permit a person to practice the full scope of this claim without undue experimentation. Therefore, these claims are invalid for lack of enablement and written description under § 112(a).

Claims 8 and 9 of the ’141 patent are invalid under 35 U.S.C. § 112 because they lack sufficient written description because the ’141 patent does not contain any description of tumors that possess “abnormal angiogenesis or hyperpermiability processes that are not p38-mediated or Raf-mediated.” *See also* ’141 Notice Letter at 23-24.

Claims 8 and 9 of the ’141 patent are invalid under 35 U.S.C. § 112 because the phrase “hyperpermiability processes” is indefinite.

Claims 8 and 9 of the '141 patent are also indefinite for lacking antecedent basis.

Claims 8 depends from claim 7. Claim 7 never recites a tumor of the kidney "that is treated," thus, claim 8 lacks antecedent basis. Claim 9 depends from claim 8, thus claim 9 suffers a similar fate.

IV. U.S. PATENT NO. 8,877,933

Plaintiffs have asserted claims 1-4, 8-10, 16-21, and 27-31 of the '933 patent. These claims generally are directed to sorafenib tosylate Polymorph I, compositions containing it, or methods of using it. The elements of these claims are described in the November 9, 2015 Notice Letter, which is incorporated by reference herein and also attached as Ex. B.

Polymorph I is described in the '933 patent as the most stable form of sorafenib tosylate at room temperature. The '933 patent reports that sorafenib tosylate can exist in the following physical forms: three polymorphs (Polymorph I, II and III) and two solvates (monomethanol solvate and monoethanol solvate).

According to the data presented in the '933 patent, metastable Polymorph II and Polymorph III will convert to Polymorph I upon heating, such as during the course of differential scanning calorimetry (DSC). Similarly, the two known solvates will desolvate and ultimately convert to Polymorph I by heating.

Sorafenib tosylate is admitted prior art to the '933 patent. The '933 patent states "sorafenib tosylate is disclosed in the prior art in WO 03/068228" ("WO 228") which was published more than one year before the priority date of the '933 patent and is therefore prior art under at least 35 U.S.C. § 102(b). WO 228 claim 22 specifically discloses sorafenib tosylate and a method of using it: "A method of treating disease mediated by VEGF-induced signal transduction pathway comprising administering N-(4-chloro-3-(trifluoromethyl) phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea tosylate." WO 228 discloses sorafenib tosylate free base and a method of making it as Example B. It also discloses 4-toluene sulfonic acid as a potential salt-forming acid. WO 228 at 15.

During the opposition to the European correspondent of the '933 patent, Plaintiffs agreed that WO 228 is the closest prior art.

According to the '933 patent, the applicant prepared sorafenib tosylate "according to a general standard method for the preparation of tosylate salts, as described in example 1 of the working examples. In this method [sorafenib] is obtained in one crystal polymorph which is referred to below as polymorph II." '933 patent at 2:14-18.

During the prosecution of the European counterpart of the '933 patent the applicant wrote:

Usually the preparation of a salt of a known compound follows a standard procedure which is e.g. solving the base and the acid in a solvent and let the resulting salt crystalizing as described in Example 1 of the present application. According to such a protocol the tosylate salt mentioned in [the WO '228 publication] can be prepared and that was initially done in our laboratories. The result was that [sorafenib tosylate] was obtained in the metastable polymorph II. That means the standard procedure yields [sorafenib tosylate] in the metastable polymorph II.

MYL_SOR00011393.

The method specifically disclosed in the '933 patent is:

Example 1

4-{4-[[{4-Chloro-3-(trifluoromethyl)phenyl}amino}carbonyl]amino]phenoxy}-N-methylpyridine-2-carboxamide tosylate in the polymorph II

903 g of 4-{4-[[{4-chloro-3-(trifluoromethyl)phenyl}amino}carbonyl]amino]phenoxy}-N-methyl-pyridine-2-carboxamide, prepared as described in WO 00/42012, are initially charged in 2700 ml of ethanol. 451.7 g of p-toluenesulfonic acid monohydrate are dissolved in 1340 g of ethanol and added dropwise at room temperature. The suspension is stirred at room temperature for 1 hour, then filtered off with suction, and the residue is washed three times with 830 ml each time of ethanol. The drying is effected at 50° C. under reduced pressure with supply of air. 1129.6 g of the title compound in the polymorph II are obtained.

'933 patent at 13:35-53.

Tosylate salts and methods preparing them were known in the prior art. *See, e.g.,* P. HEINRICH STAHL ET AL., HANDBOOK OF PHARMACEUTICAL SALTS 309-10 (2002); U.S. Patent No. 5,659,030 (crystalline cephalosporin tosylate salt); Numerous prior art reference disclose tosylate salts and methods of making them, such as U.S. Patent No. 3,065,136 (itrimin tosylate); U.S. Patent. No. 4,831,025 (sultamicillin tosylate); U.S. Patent No. US6093814 (cefdinir tosylate); WO2004072085A2 (clopidogrel tosylate); U.S. Patent No. 6,608,206 (S(-)Amlodipine tosylate); U.S. Patent No. 7,094,930 (sertraline tosylate); WO 2002/030900A (Non-deliquescent salt of 4-hydroxypiperidine derivative). *See also* Piotr Milart & Katarzyna Stadnicka, *Salts of 4-(2,4,6-Triphenyl-1-pyridinio)phenolate with p-Toluenesulfonic Acid in Molar Ratio 1:1 and 2:1 – Crystal and Molecular Structure*, Eur. J. Org. Chem 2001, 2337-2441 (2001); C.R. Noller & Poe Liang, *Para-Toluene Sulfonates as Derivatives for the Identification of Aromatic Amines*, 54 J. SOC. CHEM. IND. 670 (Feb. 1932); H.K. Hall, Jr., *Steric Effects on the Base Strengths of Cyclic Amines*, THIS JOURNAL, 5444 (May 1957).

Foreign correspondents of the '933 patent have issued in various jurisdictions. At least the European and Indian correspondents have been subject to opposition proceeding. MYL_SOR11142 -MYL_SOR00015259.

During the Indian and European oppositions of the corresponding patents, the opponents reported that all of their attempts to prepare Polymorph II according to the method disclosed in the '933 patent have failed. *See, e.g.,* MYL_SOR00012211. The disclosed method invariably produces Polymorph I. *Id.* According to Plaintiffs during the European Opposition proceedings these results are explainable because, Polymorph II is a “disappearing polymorph.” MYL_SOR00012210.

Various asserted claims include limitations to PXRD reflections, IR spectrum peak maximum, Raman spectra peak maximum, and melting point of Polymorph I. These are inherent properties of Polymorph I and therefore they add nothing to the claims for purposes of the invalidity analysis. The mere existence of Polymorph I would inherently produce a crystal form of sorafenib tosylate with the recited PXRD reflections, IR spectrum, a peak maximum,

Raman spectra peak maximum, and melting point of Polymorph I. As a result, they add nothing to the invalidity analysis of these claims. *See, e.g.*, Stephen S. Zumdahl, *Chemistry*, D.C. Heath and Company, Lexington, MA, p. 390-93 (1986).

A. ANTICIPATION

1. Inherent Anticipation Due to a “Disappearing Polymorph”

As noted above, according to information presented in the European and Indian oppositions, attempts to make sorafenib tosylate Polymorph II according to the method presented in the '933 patent have invariably resulted in the formation of Polymorph I.

All reported attempts by a POSA to make sorafenib tosylate by any of the typical methods for making tosylate salts as of the priority date would have resulted in Polymorph I. Similarly, on information and belief, attempts in the present to prepare Polymorph II by any such standard method would have resulted in the discovery of the most stable polymorph at room temperature, i.e., Polymorph I.

Attempts by a POSA to make sorafenib tosylate by any of the typical methods for making tosylate salts as of the priority date would have resulted in Polymorph I. Numerous prior art reference disclose tosylate salts and methods of making them..

Polymorph II would have converted to Polymorph I under ordinary conditions, including ordinary pharmaceutical storage conditions. Polymorph I therefore is inherently anticipated. *See SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir. 2005).

For the foregoing reasons, each of the asserted claims directed to sorafenib tosylate Polymorph I and its inherent properties are anticipated (e.g. Claims 1-4 and 27-31)

Even if asserted claims of the '933 patent are not anticipated, they are obvious over the prior art for at least the reasons stated in the November 9, 2015 Notice Letter, *id.* at 104-10, as well as for reasons set forth below.

2. **Inherent Anticipation (or Obviousness) by Standard Analytical Techniques**

Regardless of the physical form of sorafenib tosylate produced through the preparation of the salt (e.g. Polymorph II), a POSA would have conducted standard analytical techniques on the compound. Many of these techniques would have produced Polymorph I. For example, a POSA would have used any of the standard techniques to take a melting point of sorafenib tosylate, or a similar technique (DSC, hot bar, TGA, etc.) that would have inevitably produced Polymorph I.

WO 228 reports the melting point of compounds exemplified in the patent. A POSA would have understood this as an instruction to take the melting point of any compound within the scope of the patent that a POSA prepared, including sorafenib tosylate.

According to the data in the '933 patent, every known form crystalline form of sorafenib tosylate will convert to Polymorph I in the course of conventional analytical techniques. For example, based on the data presented in the patents, taking the melting point or DSC of Form 2 under ordinary conditions would have inevitably resulted in Form 1.

To the extent that this does not constitute anticipation, it would render the asserted claims obvious. A POSA would have been motivated to use these standard techniques in analyzing any form of sorafenib tosylate, even if the POSA were not specifically searching for other physical forms of sorafenib tosylate. For example, taking a melting point is almost invariably one of the first steps in characterizing a new compound.

For example, Giron (2004) states:

The melting point of organic substances is one of the first properties measured. A number of techniques are available, from immediate melting to the capillary method described in various pharmacopoeias. The substance is heated and the transition to the liquid phase is observed visually or by hot-stage microscopy. Generally the melting point is measured by DSC. Some polymorphs may have differences of melting points less than 1°C or differences more than 100°C

Giron, D et al, "Solid-State Pharmaceutical Compounds, Impact of the ICH Q6 guidance on industrial development" *Journal of Thermal Analysis and Calorimetry* 77: 709-747 (2004).

To the extent a POSA's attempts to prepare sorafenib tosylate did not initially produce Polymorph I, the use of any of these and other standard analytical techniques would have inevitably produced Polymorph I, rendering the asserted claims anticipated or obvious.

3. Anticipation by Public Use

Each of the asserted claims of the '229 patent also are invalid as anticipated or obvious due to public use in the United States before the earliest claimed priority date. [REDACTED]

[REDACTED]

[REDACTED] Therefore, each of the asserted claims is anticipated or obvious.

B. Obviousness

Each of the asserted claims of the '299 patent is invalid as obvious over the prior art described above and in this section. To the extent that the asserted claims are not rendered anticipated or obvious as described above, the asserted claims are nevertheless obvious.

A POSA would have been strongly motivated to identify the most stable form of sorafenib tosylate, would have had a reasonable expectation of success in doing so, and would have selected that most stable form for pharmaceutical development and use.

1. Scope and Content of the Prior Art

The scope and content of the prior art, as well as the differences between the claims and the prior art, is described above in, e.g., the sections describing the background of the patent and anticipation. The scope and content of the prior art, as well as differences between the claims and prior art, is further described below.

2. Motivation to Identify the Most Stable Form and Expectation of Success in Obtaining the Most Stable Polymorph

A POSA as of the priority date would have been strongly motivated to investigate crystal forms of sorafenib tosylate and, in particular, identify the most stable form. *See Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*, FOOD AND DRUG ADMINISTRATION (February 1987). As of the priority

date, sorafenib tosylate was a drug undergoing clinical development and Plaintiffs were seeking approval to market it as a drug for human use in the United States and other countries.

During the prosecution of the corresponding European patent, Plaintiffs stated:

It is very important for a pharmaceutical product to have always the same constant properties. Therefore there is a need to find the most stable form of a compound because only the most stable form can ensure that all properties and characteristics regarding stability, solubility, shelf life and bioavailability maintain constant during manufacturing, storage and administration. . . .

The metastable forms have different shelf lives, solubilities and bioavailabilities and due to its metastability they have the tendency to change into different forms having different properties. **For a pharmaceutical product it is important to have always the same constant properties. Only the stable form according to the present invention can ensure these constant properties.**

MYL_SOR00011392 (emphasis added).

Plaintiffs also wrote:

Since pharmaceutical compositions shall have the same reliable form for the active ingredient having the same reliable and constant properties, there is the need to use the stable polymorph.

MYL_SOR00011393.

[REDACTED]

[REDACTED]

3. A POSA Would Have Had an Expected Sorafenib Tosylate to Exhibit Polymorphism

A POSA would have expected that sorafenib tosylate would have exhibited polymorphism and would have had a reasonable expectation of success in identifying the most stable polymorph.

A very large fraction of pharmaceutical compounds demonstrate polymorphism. *See* Haleblan and W. C. McCrone, “Pharmaceutical Applications of Polymorphism” *J. Pharm. Sci.*, 58, 911-29 (1969) at 912: “The scientific literature also included numerous indications of [polymorphism’s] importance in pharmaceuticals. . . . It is now apparent that most, if not all,

compounds and elements show a variety of different crystal forms.” As one of the inventors, Dr. Grunenberg has written, “Polymorphism occurs frequently in organic compounds. It has been shown that about 80% of drug substances are polymorphic.” Grunenberg, A. et al. “Theoretical derivation and practical application of energy/temperature diagrams as an instrument of preformulation studies of polymorphic drug substance,” *International Journal of Pharmaceutics*, 129 147-158 (1996) (citing Grunenberg, A., Thermische Methoden, Thermoanalyse, In Apothekammer Nordrhein (Ed.), Regelweiterbildungsseminat Pharmazeutische Analytik, Bonn, 1992, pp. 18.).

Walter McCrone states, “It is at least this author’s opinion that every compound has different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound.” W. C. McCrone, “Polymorphism” Chapter 8 in *Physics and Chemistry of the Organic Solid State*, Interscience Publishers, New York, NY (1965) at 727.

Numerous authors have either cited this statement by McCrone or have quoted him directly. In his 1987 chapter on conformational polymorphism Bernstein quotes McCrone directly, prefacing the quote by stating:

Because of its industrial importance, examples of polymorphism and techniques for investigating and utilizing it come from those areas of chemical research where full characterization of a material is crucial in determining its ultimate use, e.g. in pharmaceutical, dyes, and explosives. Various aspects of the subject have been treated in books and a number of reviews. The ubiquity of the phenomenon is still not generally recognized, although over twenty years ago McCrone suggested that virtually “every compound has different [sic] polymorphic forms...the number of forms for a given compound is proportional to the time and energy spent in research on that compound.”

See J. A. Bernstein, “Conformational Polymorphism,” in *Organic Solid State Chemistry*, G. R. Desiraju, ed., Elsevier, Amsterdam, 471-518 (1987) at p. 472.) (“Bernstein (1987)”).

Bernstein quotes this same passage in the introduction to his 2002 book entitled “Polymorphism in Molecular Crystals” (J. A. Bernstein, Oxford University Press, Oxford,

2002, p. 8). Clearly, already by 1987, Bernstein recognized the industrial importance and “ubiquity” of polymorphism. By 2002, when his book on polymorphism was published, the importance and ubiquity of polymorphism were even more established and widely recognized in the field of pharmaceutical chemistry.

Bernstein’s sentiments are echoed by numerous authors, including Guillory and Caira. Guillory, while citing the 1965 McCrone article, quotes an equivalent statement from a 1957 publication by McCrone: “Those who study polymorphism are rapidly reaching the conclusion that all compounds, organic and inorganic, can crystallize in different forms or polymorphs. In fact, the more diligently any system is studied, the larger the number of polymorphs studied.” Guillory (1999) at 185. Guillory prefaces this quote with a provocative question:

One question that is likely to arise during the registration process is “What assurance can be provided that no other crystalline forms of this compound exist?” It is incumbent on the manufacturer of a new drug substance to show that due diligence has been employed to isolate and characterize the various solid-state forms of a new chemical entity. This may seem to be a daunting task, particularly in light of the widely quoted statement by Walter C. McCrone [2] that ...

Guillory (1999) at 185.

Caira (Mino R. Caira, “Crystalline Polymorphism of Organic Compounds,” *Top. Curr. Chem.*, E. Weber, Ed., **198**, 163-208 (1998) at p. 166) (“Caira (1998)”) paraphrases McCrone in a way that makes it clear that the *absence* of polymorphism is unexpected and difficult to demonstrate:

Demonstrating the absence of a tendency to polymorphism is not easy; most substances when investigated for a sufficiently long time will reveal more than one polymorph [42].

Therefore, it would have been reasonable to expect a given compound to follow this general rule, including sorafenib tosylate.

In 1990, Borka and Halebian had published an extensive list of over 470 pharmaceutically important compounds that exhibited polymorphism. See L. Borka and J. K. Halebian, “Crystal Polymorphism of Pharmaceuticals,” *Acta Pharm. Jugosl.* **40**, 71-94 (1990).

In Chapter 7 of his book, *Polymorphism in Molecular Crystals*, Bernstein cites this paper as well as other large compilations of pharmaceutical crystal forms, including that of over 559 crystal forms reported by Griesser and Burger in 1999. Clearly, by 2002, when this book was published, those in the pharmaceutical field were well aware of the prevalence of polymorphism. Raw also teaches that identification of polymorphs is important in the pharmaceutical industry:

Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences, which may result in product development delay and commercial production... As a result, pharmaceutical solid polymorphism has received much scrutiny throughout various stages of drug development, manufacturing, and regulation. For these reasons, it is essential that during drug product development and ANDA regulatory review, close attention be paid to pharmaceutical solid polymorphism.

Raw, *et al.*, “Regulatory Considerations of Pharmaceutical Solid Polymorphism in Abbreviated New Drug Applications,” *Adv. Drug. Deliv. Rev.*, **56**, 397-414 (2004).

Giron states that “Investigating the polymorphic behavior of drugs and excipients is an important part of preformulation work.” Giron (1995) also provides an extensive list of polymorphism and pseudo-polymorphism found in the literature. Giron, D. “Thermal analysis and calorimetric methods in the characterization of polymorphs and solvates.” *Thermochimica Acta* 248 1-59 (1995).

Given that many compounds commonly exhibit polymorphism, the skilled artisan would have been motivated to determine whether sorafenib tosylate can exist in multiple polymorphic states in order to exploit potentially favorable properties of one polymorph versus others, and would not have found it unexpected that sorafenib tosylate does exhibit polymorphism.

4. A POSA Would Have Been Motivated to Search for Polymorphs

“Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances,” was published by Center for Drug Evaluation and Research

(“CDER”), Food and Drug Administration, Department of Health and Human Services, in February 1987 (“FDA Guideline 1987”). The purpose of FDA Guideline 1987 is to provide applicants with acceptable procedures for complying with regulations regarding the production of new drug substances, specifically, drug substances manufactured by chemical synthesis. *See* FDA Guideline 1987 at 1. FDA Guideline 1987 teaches that the quality and purity of the drug substance cannot be assured solely by end-of-the-line testing, but depends on proper control of the manufacturing and synthetic process as well. *See id.* at 2. FDA Guideline 1987 further teaches that a particular synthetic pathway will typically be uniquely associated with a set of impurities. *See id.* at 4. As set forth in the FDA Guideline 1987, FDA’s “regulations [for the manufacture of drug substances] require specifications and analytical methods ... to help assure that the proper identity, strength, quality, and purity of the drug substance have been attained and are consistent from batch to batch.” *Id.* at 25. With respect to impurities, FDA Guideline 1987 states that “[i]mpurities should not only be detected and quantitated, but should also be identified and characterized when this is possible with reasonable effort” and that “[a]ll major impurities should be individually limited.” *Id.* at 26-27.

a. Regulatory and Industry Realities

Because sorafenib tosylate was a drug candidate, a POSA would have been motivated by regulatory requirements in the United States and other countries, and the realities of pharmaceutical development to attempt to identify the most stable polymorph. *See* FDA Guideline 1987. In fact, because Bayer was already seeking regulatory approval in the United States, a POSA would have assumed that Bayer had already conducted a polymorph study, had already identified the most stable form and likely selected it for use in its product. [REDACTED]

[REDACTED]

Different forms of molecular solids, including crystalline polymorphs, crystalline solvates, and amorphous materials, display unique properties, many of which could affect the compound's performance as a pharmaceutical. For example, forms may vary in terms of chemical properties such as solubility, dissolution rate, and bioavailability, as well as bulk properties, such as chemical stability, ease of filtering and drying, and flowability. *See* Threlfall (1995) at p. 2436. For example, polymorphs of the diabetes drug chlorpropamide have very different dissolution profiles and crushing strength, properties that affect both the administration and manufacture of this and other pharmaceuticals. *See* Byrn (1999) at 178, 274. Thus, the discovery or preparation of a polymorph or new polymorphs of a known compound is an important consideration for drug development. The strong motivation for drug companies to discover polymorphs has been recognized in the literature. *See, e.g.*, Bernstein (2002), pp. 27, 255, 297–298; *see also* Guillory, (1999) at pp. 184-185.

Beginning in 1987, the FDA's Guidelines For Submitting Supporting Documentation In Drug Applications For The Manufacture Of Drug Substances required polymorph screening and identification for solid dosage forms or suspension drug products. In particular, the Guidelines state:

A person of ordinary skill in the art would understand that FDA's Guidelines: regulations require, where appropriate, specifications characterizing the drug substance so as to assure the bioavailability of the drug product (*See* 21 CFR 314.50(3)(ii), and 320.52(e) [4-1–85 edition]). Certain solid-state properties of the drug substance (*e.g.* polymorphic form or amorphism, solvation or hydration, various types of inclusion complexes, and particle size or surface area) may profoundly affect dissolution and bioavailability from solid dosage forms or suspension drug products.

FDA Guideline 1987 at 31. The FDA goes on to instruct that “[a]ppropriate analytical procedures should be used to determine whether (or not) polymorphism occurs.” *Id.* at 34. The FDA required drug products to be designed to guarantee that the solid-state form would not change. In particular, FDA states that information should be provided to ensure that:

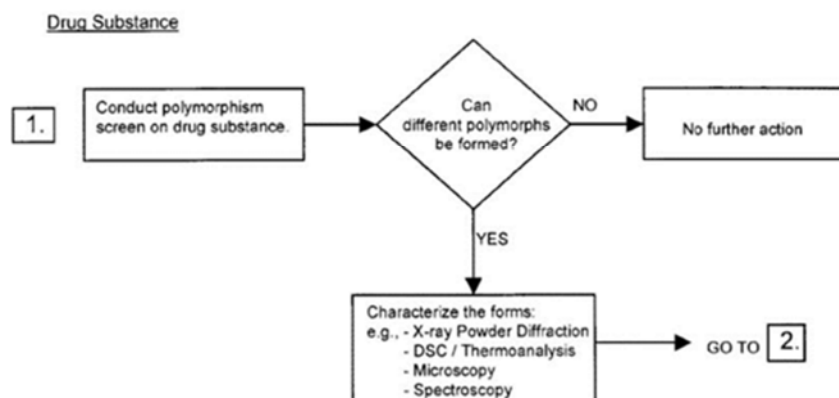
- (a) a change in solid-state form does not occur when the drug substance is manufactured and stored according to the NDA directions; or]

- (b) different forms occur but do not result in a bioavailability problem; or
- (c) polymorphism, solvation, or particle size has an important effect on bioavailability.

FDA Guidelines 1987 at 33. In addition, the FDA guidance from December 2000 explained that “[d]ifferences in these [polymorphic] forms could, in some cases, affect the quality or performance of the new drug products.” *See* FDA Guidance on Q6A Specification, 65 Federal Register 83041, 83046 (2000); *see also* ICH Harmonised Tripartite Guideline, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances Q6A (1999) at p.8. These guidelines mention drug product stability and bioavailability as areas where different polymorphic forms could cause different results. *See* FDA Guidance on Q6A Specification (2000) at 83046; ICH Guideline Q6A (1999) at p.8.

The FDA Q6A Specification specifically recommends that applicants conduct a polymorphic screen as the first step in investigating the need to set acceptance criteria for polymorphism in drug substances. *See* FDA Guidance on Q6A Specification (2000) at 83046, 83055; ICH Guideline Q6A (1999) at pp. 8-9, 24.

DECISION TREE #4: INVESTIGATING THE NEED TO SET
ACCEPTANCE CRITERIA FOR POLYMORPHISM
IN DRUG SUBSTANCES AND DRUG PRODUCTS



Caira
regulatory
of pharmaceutical manufacturers to provide evidence for the occurrence or absence of
polymorphism in a given product. Caira states:

notes the
requirement

Already, legislation requiring drug manufacturers to provide information relating to the occurrence (or apparent absence) of polymorphism in their products has been introduced [41]. Demonstrating the absence of a tendency to polymorphism is not easy; most substances when investigated for a sufficiently long time will reveal more than one polymorph [42].

Caira (1998) at 166. Caira also states: “A recent analytical study stresses the growing need, prompted partly by legislative requirements, to differentiate polymorphs and to quantify polymorphic mixtures in pharmaceutical production [126].” Caira at 189.

Threlfall echoes these sentiments:

Much of the literature on polymorphism of organic compounds relates to pharmaceutical products. The incentive for this interest in polymorphism began with the need to satisfy regulatory authorities in various countries as to the bioavailability of formulations of new chemical entities.

Terence L. Threlfall, *Analysis of Organic Polymorphs*, 120 ANALYST 2435, 2436 (1995)

(“Threlfall (1995)”). Byrn notes that “[i]nterest in the subject of pharmaceutical solids stems in part from the Food and Drug Administration’s (FDA’s) drug substance guideline that states ‘appropriate’ analytical procedures should be used to detect polymorphic, hydrated, or amorphous forms of the drug substance. These guidelines suggest the importance of controlling the crystal form of the drug substance.” Byrn, *Pharm. Res.*, 12, 945-954 (1995) at 945.

Vippagunta notes that:

Because different crystalline polymorphs and solvates differ in crystal packing, and/or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physical properties, such as density, hardness, tabletability, refractive index, melting point, enthalpy of fusion, vapor pressure, solubility, dissolution rate, other thermodynamic and kinetic properties and even color [12]. Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products [13], while differences in solubility may have implications on the absorption of the active drug from its dosage form [14], by affecting the dissolution rate and possibly the mass transport of the molecules. These concerns have led to an increased regulatory interest in understanding the solid-state properties and behavior of drug substances. For approval of a new drug, the drug substance guideline of the US Food and Drug Administration (FDA) states that

“appropriate” analytical procedures need to be used to detect polymorphs, hydrates and amorphous forms of the drug substance and also stresses the importance of controlling the crystal form of the drug substance during the various stages of product development [11]. It is very important to control the crystal form of the drug during the various stages of drug development, because any phase change due to polymorph interconversions, desolvation of solvates, formation of hydrates and change in the degree of crystallinity can alter the bioavailability of the drug. When going through a phase transition, a solid drug may undergo a change in its thermodynamic properties, with consequent changes in its dissolution and transport characteristics [15].

Sudha R. Vippagunta, Harry G. Brittain, and David J. W. Grant, “Crystalline Solids,” *Adv. Drug Deliv. Revs.*, 48, 3-26 (2001)) at pp. 4-5.

Further, Beckmann wrote in 2000:

As concerns the pharmaceutical industry, it has been shown that more than half of the drug substances described in monographs crystallise in more than one solid state form, being it either polymorphs, solvates, or both.¹ The solid state form of a drug substance can influence a variety of properties, namely the solubility and rate of dissolution or the chemical stability or stability against excipients. Thus, the regulatory bodies require an exhaustive search for polymorphic forms of a drug substance

Beckmann, W. “Seeding the Desired Polymorph: Background, Possibilities, Limitations, and Case Studies,” *Organic Process Research & Development* 4, 372–383 (2000).

b. Need to Understand the Energy Landscape

A POSA also would have been motivated to search for the most stable polymorph in general in order to understand the energy landscape of the sold forms of the compound. *See., e.g.* Grunenberg, A. et al. “Theoretical derivation and practical application of energy/temperature diagrams as an instrument of prefomulation studies of polymorphic drug substance,” *International Journal of Pharmaceutics*, 129 147-158 (1996).

In his 2002 book, “Polymorphism in Molecular Crystals,” Bernstein highlights the importance of screening a compound for polymorphic behavior and the necessity of understanding the energy landscape for both the stable and metastable forms that one is able to generate. Bernstein (2002) at 252-253. This alone would provide more than enough

motivation for one skilled in the art to initiate a solvent screen and other methods designed to find as many polymorphs of sorafenib tosylate as possible.

The lower solubility of stable forms may limit their pharmacological utility (*e.g.* ritonavir (Chemburkar *et al.* 2000; Bauer *et al.* 2001)), so that it may be advantageous to selectively obtain and maintain a metastable form in a formulation (*e.g.* Shah *et al.* 1999). In such cases, crystallization strategies may be designed on the basis of the principles derived from the energy-temperature or pressure-temperature diagrams (Toscani 1998), as described in Chapter 3. It will be recalled that even if qualitative in many aspects, such diagrams serve to summarize a great deal of information in a very compact manner. For instance, characterization of the two polymorphs of taltireline, a central nervous system activating agent, indicated that they were enantiotropic, but the α form, metastable at its crystallization temperature of 10° C, was preferred for formulation. Critical evaluation of the crystallization parameters isolated the factors that led to conversion of the stable form, and these were controlled to prevent conversion (Maruyama *et al.* 1999). For a two-component system generation of the phase diagram can also prove very useful in developing strategies for obtaining a number of crystal modifications, including a metastable one (Henck *et al.* 2001).

Together with knowledge of the phase diagram an increasing variety of techniques have been designed and employed to generate metastable modifications. Seeding of course, is one of those strategies, and Beckmann *et al.* (1998) developed a seeding strategy for a batch cooling crystallization to obtain quantitatively and reproducibly a metastable form of abecarnil, regardless of the purity of the material. In another approach, after thorough characterization of three polymorphic modifications by a variety of analytical methods, a desired metastable form of (R, S)-proxyphylline was crystallized in gram quantities from the supercooled melt, and proved to have considerable kinetic stability under dry atmospheric conditions (Griesser *et al.* 2000). A variation on that same theme was the successful high-temperature crystallization from the amorphous material of the metastable a form of indomethacin, whereas the low temperature crystallization yielded the stable γ form (Andronis and Zografi 2000).

One traditional strategy for screening a compound for polymorphic behaviour involves the trial of a variety of solvents and solvent mixtures. Our understanding of the role and choice of solvent has improved considerably and this information, combined with a knowledge of zones of stability can aid in determining crystallization conditions for obtaining metastable form (Threlfall 2000). In addition, there has also been considerable progress in understanding and utilizing the interactions of solvent with the growing crystal (Weissbuch *et al.* 1991; Lahav and Leiserowitz structure determinations of polymorphs with crystal morphological data (*i.e.* crystal habit, and the orientation of molecules projecting from the particular faces exposed) and with known intermolecular interactions between solute molecules and solvent functional groups allows the rational choice

of solvent to select a particular polymorphic form (Weissbuch *et al.* 1995). An analysis of this nature was carried out and experimentally confirmed by Blagden *et al.* (1998a, b) for polymorphic modification of sulphathiazole.

This is clearly an area where the combination of thermodynamic, kinetic and structural information potentially can lead to successful strategies for controlling the polymorphic form obtained, in specific instances a metastable form, and as the means for obtaining these data become more sophisticated the approaches described here are sure to be developed and expanded (*See also* Section 3.7)

Bernstein (2002) at 252-253 (emphasis added).

Giron (2004) also states:

Precise knowledge of thermodynamic stability and relationships between different solid phases is a pre-requisite for the manufacture of robust drug substance and drug products. It is also necessary to know the equilibration curves between the solid forms under the influence of the parameters humidity, temperature and pressure in order to predict changes for storage, stability, compatibility and pharmaceutical processes. The major hurdle for the pharmaceutical industry is to have to recall medicines because of polymorphism problems as it was the case for Ritonavir.

Giron (2004) at 710.

c. A POSA Would Have Been Specifically Motivated to Use Thermal Evaluation Techniques

[REDACTED]

[REDACTED]

Thermal techniques including hot stage or thermal microscopy, DSC, and TGA have been employed for decades in the pharmaceutical industry to assess transitions between crystal forms. Byrn 1999 at 279; Caira at 178; Halebian at p. 918; Threlfall at 2439 and 2446.

Byrn provides the following flowchart/decision tree, which specifically identifies DSC and other thermoanalytical methods as part of the standard process of polymorph identification.

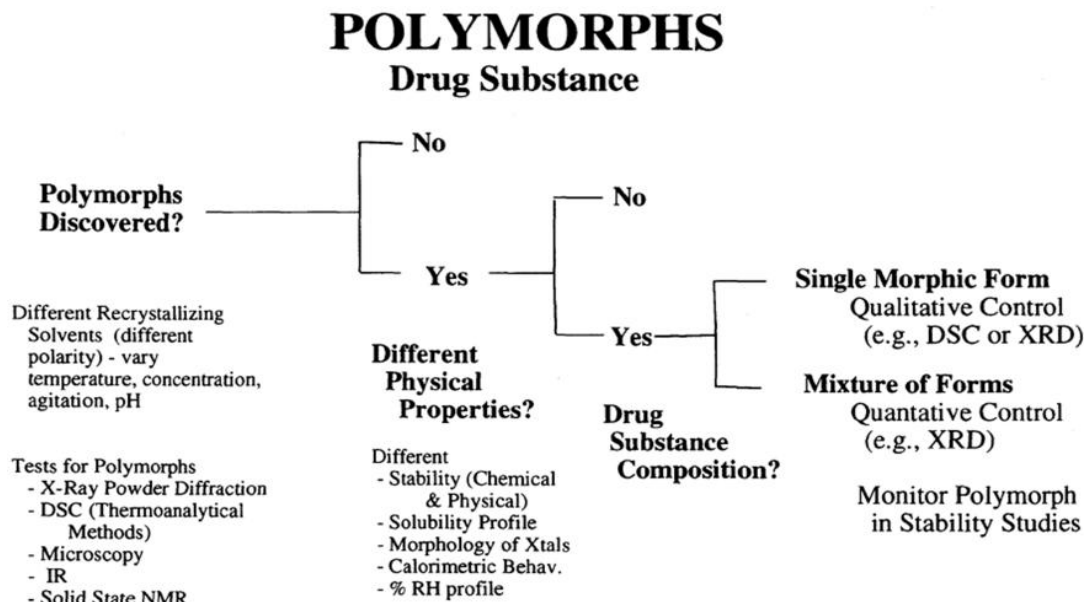


Figure 1. Flow chart/decision tree for polymorphs.

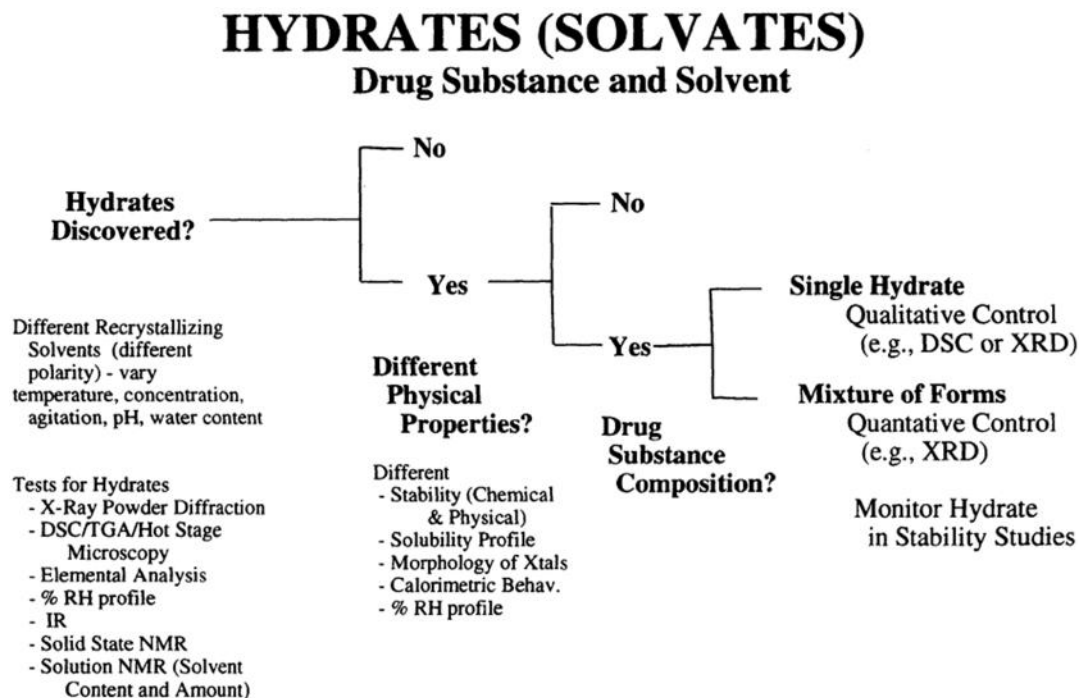


Figure 6. Flow chart for solvates or hydrates.

Based on the knowledge of a POSA, as exemplified in the literature references discussed above, it would have been obvious to a POSA to use melting point, hot-stage microscopy, DSC, or TGA to assess the relative thermal stability of any crystal form that he or she prepared. This would have inevitably produced Polymorph I.

i. Melting point

One method of characterizing crystal forms is by taking a melting point. It is often possible to distinguish two polymorphic forms by their melting points, especially when the melting points are well separated. *See, e.g.* Giron (2004)

ii. Hot-Stage Microscopy

Hot-stage microscopy has been employed for decades in the pharmaceutical industry to assess transitions between crystal forms. In this method, the sample is heated gradually on a microscope stage while events are recorded visually or with either photographs or videos. This is a convenient technique that allows a scientist to visually observe and record phase changes as

a function of temperature. Hot-stage microscopy is often used in conjunction with differential scanning calorimetry (“DSC”).

Threlfall recognizes that hot stage microscopy is a technique for generating polymorphs. In particular, he states: “hot-stage microscopy has been often so used and remains the outstanding method for the examination and generation of polymorphs.” Threlfall (1996) at 2439. He further states:

A preliminary examination under a binocular microscope will enable the overall characteristics of the sample to be ascertained. Temperature cycling and melt and solvent recrystallization experiments with a polarizing microscope equipped with a hot-stage will allow the identification of transition points, the distinguishing of monotropic and enantiotropic relationships, estimation of the tendency of melts and individual phases to supercool, ***the generation of stable and unstable polymorphs*** and the recording of their optical properties. The identification of solvates and the observation of sublimates and of any tendency to decompose are added information. This can be carried out with minute amounts of material. The field has been excellently and comprehensively reviewed in the past, and for that reason only the developments since then will be considered in detail here.

Threlfall at 2439 (emphasis added); *See also* Byrn (1999) at 279; Caira (1998) at 178; Haleblan (1969) at 918. Thus, hot stage microscopy is an important tool for investigating polymorphism of crystalline solids.

iii. Differential Scanning Calorimetry (“DSC”)

Differential Scanning Calorimetry (“DSC”) is a type of test that can be used to measure the melting point of a material. DSC uses the thermal characteristics of different phase transitions to distinguish between different materials. In DSC, one applies enough thermal energy (or power) to the sample and a reference to keep them at the same temperature while warming or cooling. The DSC data is in the form of a curve showing the heat flow as a function of sample temperature. The direction of the peak (which is either endothermic or exothermic) helps to identify the type of transformation taking place.

The DSC trace complements the melting point by providing detailed information about the melting transition, including the enthalpy of fusion (i.e., the heat energy that must be added

to melt a specific amount of the substance), which is a characteristic property of each crystalline form. The DSC can provide diagnostic information related to pre-melting behavior, phase transitions, decomplexation of bound solvent, and chemical decomposition.

In particular, DSC is used throughout the pharmaceutical industry to identify new crystalline forms of drug substances. Both desolvation and solid-solid phase transformations give rise to signals in the DSC trace and would prompt further investigation of the crystal forms generated by these thermal processes. *See, e.g., Shami, E. et al* “Preformulation” in *Theory and Practice of Industrial Pharmacy* (1976) at 4 (worksheet for summarizing data, and noting melting point and DSC in particular).

iv. Thermogravimetric Analysis (“TGA”)

In a thermogravimetric analysis (or thermogravimetry), the mass of a compound is monitored as a function of temperature. Typically, a known amount of sample is heated at a constant rate, and the loss of mass due to decomposition or evaporation is recorded as a function of time while an inert gas is flowed past the sample. Both the mass of the sample and the first derivative (mass loss per temperature unit) are plotted as a function of temperature.

v. Drying

In any organic synthesis that generates a final product, the sample is dried so that the yield can be reported and the sample can be analyzed. New compounds in particular are subjected to elemental analysis, which requires a dried sample (i.e., with no solvent, if possible). Wiberg describes the necessity for engaging in the drying process. He states: “After recrystallization it is usually necessary to dry the material.” Wiberg (1960) at pp. 109-110. Thus a POSA would have dried any sample of sorafenib tosylate produced, which would have inherently produce Polymorph I.

d. A POSA Would Have Been Specifically Motivated to Conducted a Polymorph Screen

As noted in Plaintiffs’ statements to the European Patent Office, POSA would have been motivated to seek the most stable polymorphic form of sorafenib tosylate because that

form would be unlikely to convert to a different polymorphic form that could negatively impact a drug product's quality or performance.

There are numerous references that demonstrate motivation and knowledge. For example, in his chapter entitled, "Preformulation," Fiese, *et al.*, states:

During preformulation, it is important to identify the polymorph that is stable at room temperature and to determine whether polymorphic transitions are possible within the temperature range used for stability studies and during processing (drying, milling, etc.).

Eugene F. Fiese, *et al.*, Chapter 8 in *The Theory and Practice of Industrial Pharmacy*, Lachman, *et al.*, Eds., Lea & Febiger, 171-96 (1986) at pp. 180-81.

Caira explains that when developing a new drug product, "[s]ystematic investigation of a compound to determine whether it is prone to polymorphism . . . is routine practice in pharmaceutical pre-formulation studies. Identification of the different polymorphic forms of a drug substance . . . [is] essential for ensuring drug preparations with reproducible behaviour." Caira at 165-66.

Similarly, Guillory explains that "[i]t is incumbent on the manufacturer of a new drug substance to show that due diligence has been employed to isolate and characterize the various solid-state forms of a new chemical entity." Guillory at 185.

Threlfall further explains:

As formulations have become more sophisticated and as the tolerances on products have become tighter, the need to identify polymorphic behaviour at an early stage of development has become important in the pharmaceutical industry as a means of ensuring reliable and robust processes and conformity with good manufacturing practice. The aim is to avoid, *inter alia*, tableting problems and subsequent tablet failure, crystal growth in suspension and resultant caking, precipitation from solutions and problems with suppositories, as well as chemical production problems such as filtrability and to ensure analytical reproducibility.

Threlfall (1995) at 2436.

Byrn provides further motivation to conduct studies of polymorphism of pharmaceuticals in section 13.3 of his book at 266-278. Byrn (1999). Here, he cautions the

reader that changes in polymorphic form might affect the solubility and bioavailability of the pharmaceutical:

13.3 POLYMORPHIC TRANSFORMATIONS OF PHARMACEUTICALS

In this section, studies of drugs that undergo polymorphic transformation are reviewed and discussed. This is an important area of research because of its implications in the physical stability of drug dosage forms. As mentioned earlier, different polymorphs possess different physical properties-solubility and bioavailability being the most important. In addition, keep in mind that changing the temperature or pressure during a manufacturing operation, such as tableting, could induce a polymorphic transformation.

Byrn (1999) at 266. *See also* Shami, E. *et al* “Preformulation” in *Theory and Practice of Industrial Pharmacy* (1976) at 3 (“Investigating the polymorphic properties is important, since polymorphic forms in many cases exhibit differences in biological availability.”).

The vast majority of drugs use the most stable form of the drug as the commercial active pharmaceutical ingredient. In the context of pharmaceuticals, the most stable polymorphic form is a preferred form, because, for example, it can extend the shelf life of the drug. Haleblan (1969) at 912-13; MYL_SOR0012929.

The most stable form is most frequently chosen for commercial development because of risk of conversion.

The goal in any industrial pharmaceutical organization is to have the thermodynamically preferred polymorph or solvate present in the first scaled-up batch of drug substance. If this situation is achieved, then all toxicology, pharmacokinetic, and clinical studies will be conducted with the crystalline form that is likely to be the commercial form of the drug substance. This will eliminate expensive retesting should a more stable but previously unknown polymorph appear. Prudent drug development programs will identify the preferred crystalline form early in development, with a polymorph/salt group working in close conjunction with process chemists to make the thermodynamically preferred polymorphic form the initial kilogram-scale batch. They will also identify and define the physicochemical boundaries of that polymorph.

Harry G. Brittain and Eugene F. Fieser, “Effects of Pharmaceutical Processing on Drug Polymorphs and Solvates,” in *Polymorphism in Pharmaceutical Solids*, Harry G. Brittain, Ed., Marcel Dekker, Inc., New York, NY, 331-361 (1999)) at 358.

Accordingly, the goal of understanding the thermodynamic relations between the different crystal forms, and in particular the relation of other forms to the most thermodynamically stable polymorphic form of a drug substance, is a significant consideration during drug product development.

Caira cites safety reasons for the control of crystal form used in pharmaceuticals: Solubility and dissolution rate analyses are of vital importance for polymorphs and pseudopolymorphs of pharmaceutical relevance. For a given drug, metastable polymorphs tend to have higher solubilities and faster dissolution rates than the stable polymorph. When metastable forms are employed in solid dosage forms (tablets, capsules), they generally yield higher and earlier blood serum levels [25]. Thus, for potent drugs with a narrow therapeutic index (*e.g.* the cardiotonic digoxin), inadvertent use of a metastable polymorph in a tablet could result in patient death from overdose. In vitro dissolution testing is therefore carried out routinely as part of the quality control of manufactured tablets and capsules.

Caira (1998) at 165-66.

Guillory urges early assessment of the relative stabilities of different crystal forms because of the possibility of conversion from a metastable form to a more stable one:

It is essential to ascertain whether the crystalline material that results from a synthetic procedure is thermodynamically stable before conducting pivotal trials, since a more stable form may be obtained subsequently, and it may be impossible to produce the metastable form in future syntheses. Conversion from one polymorph to another can occur during processing or upon storage.

Guillory (1999) at 184.

Repeating these same principles, Yu explains that:

The widespread existence of polymorphic drugs underscores the importance of an efficient and consistent characterization strategy. The potential impact of changing crystal forms during late-stage development in terms of cost and product delay justifies the systematic and early characterization of polymorphism.

See L. Yu, “Physical characterization of polymorphic drugs: an integrated characterization strategy,” PSTT, 1, 118-27 (1998) at 125-26 (“Yu (1998)”).

It was known in the art as of the priority date that polymorph screening was necessary to ensure consistent, bioavailable, and stable drug product, as Plaintiffs themselves admitted. It was also known that the consequences of not investigating the relative stabilities of different

crystal forms and their ease of conversion could be devastating, both for the manufacturer, and, in some cases, for public health. In 1996, Abbott Laboratories began to market a semi-solid capsule of ritonavir (NorvirTM), which was an important protease inhibitor used in the fight against HIV/AIDS. Because of its low bioavailability and low solubility, ritonavir was formulated in an ethanol/water solution. In 1998, after 240 lots had been produced without any solubility problems, certain capsules began to fail the dissolution tests as a new, more stable polymorph emerged. S. Chemburkar, “Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development,” *Organic Process Research & Dev.*, 4, 413-417 (2000) at 413. Soon thereafter, it was no longer possible to generate the original metastable form as “seeds” of the more stable form infiltrated laboratories and manufacturing plants. *Id.* The sudden appearance of this stable form of ritonavir and the great difficulty in manufacturing the metastable form required Abbott to remove ritonavir from the market for over a year as it searched for a new formulation. *Id.*; see also Bauer, J. et al, “Ritonavir: An Extraordinary Example of Conformational Polymorphism,” *Pharmaceutical Research*, 18, 6 859-866 (2001).

The prior art experience with ritonavir presents a cautionary tale that the pharmaceutical industry has taken to heart. Chemburkar (from Abbott) writes: “It is highly advisable to put enough resources to carry on exhaustive research to identify the most stable and all possible polymorphs.” Chemburkar at 417. See also Bauer, J. et al, “Ritonavir: An Extraordinary Example of Conformational Polymorphism,” *Pharmaceutical Research*, 18, 6 859-866 (2001) at 859 (noting that because ritonavir was in ethanol/water solution “no crystal form control was required” under the then-operative ICH guidelines).

Thus a POSA as of the priority date would have been keenly aware of the necessity of performing a polymorph screen and identifying the most thermodynamically stable polymorph of a drug substance such as sorafenib tosylate.

A POSA would therefore have been specifically motivated to attempt to identify the most stable polymorph of sorafenib tosylate.

e. Solution-Mediated Transformations and “Slurrying”

As noted above, a POSA would have been motivated to find the most stable form of sorafenib tosylate for pharmaceutical development.

In practice, the simplest and most typical way of searching for the most stable crystal form involves a “slurry conversion,” in which the different crystal forms of a particular compound are rapidly stirred over a period of hours or days in the presence of solvent sufficient to dissolve only a small amount of the substance in question. Haleblan (1969) at 922.

Because the most thermodynamically stable polymorph generally has the lowest solubility, this process, which typically involves dynamic dissolution and recrystallization, can be used to convert less stable polymorphs into the most thermodynamically stable polymorph. Threlfall (1995) at 2449 (“The solubility also has an important thermodynamic feature: it is inversely related to the stability of the polymorph such that the most stable polymorph is always the least soluble at a given temperature.”).

A POSA would understand that a reliable way of identifying the most stable crystal form of sorafenib tosylate would be to slurry any of the solid forms that might be generated in several different solvents and to compare the results of these slurries by using powder X-ray diffraction. *See, e.g.* Gu, C-H et al. “Polymorphic Screening: Influence of Solvents on the Rate of Solvent-Mediate Polymorphic Transformation”, *Journal of Pharmaceutical Sciences* 90, 11 1878-1890 (2001). PRACTICAL PROCESS RESEARCH & DEVELOPMENT, authored by Neal G. Anderson, was published by Academic Press in 2000 (“Anderson”). Anderson teaches the general practice in many aspects of process research and development, and particularly pharmaceutical process research and development, including process optimization, purification and control of impurities. *See* Anderson, Chapters 8 and 11. For example, Anderson teaches techniques for optimizing reactions to minimize impurities and “tools for purifying the product by column chromatography, crystallization and reslurrying.” *Id.*

Caira cites earlier literature on solvent-mediated transformations, whose driving force is the difference in solubility between different forms:

Theoretical and experimental studies of the role of solvent on polymorphic crystallization and phase transformations abound in the literature of the last few years and some pertinent examples are described here. For solvent-mediated transformations, the driving force is the difference in solubility between different polymorphs. An important earlier paper on the kinetics of such phase transformations [51] described a model featuring two kinetic processes in solid to solid phase changes via a solution phase, namely dissolution of the metastable phase and growth of the stable one.

Caira (1998) at 169.

Grant also discusses the use of solution-mediated phase transformations of metastable polymorphs to give more stable ones:

Under appropriate thermodynamic conditions discussed at the beginning of this chapter, a less stable polymorph may be converted into a more stable polymorph. The rate of conversion to the more stable polymorph is often rapid, if mediated by the solution phase or vapor phase. In these phases the less stable polymorph (having the greater solubility or vapor pressure) dissolves or sublimates, while the more stable polymorph (having the lower solubility or vapor pressure) crystallizes out.

Grant (1999) at 26.

Rodriguez-Hornedo provides the same sentiments:

Knowledge of the propensity of a metastable solid phase to dissolve in a liquid phase from which a stable solid phase nucleates and grows is crucial in many stages of pharmaceutical development, because pharmaceutical solids are designed to be dissolved and to come in contact with solvents since the early stages of development (isolated by crystallization from solution) and during processing (wet granulation, spray-drying, freeze-drying, etc.). Given that the sudden disappearance or appearance of a crystalline modification can threaten process development, characterization of the kinetics and mechanisms of solvent-mediated transformations is of practical importance.

Naír Rodríguez-Hornedo and Denette Murphy, “Significance of Controlling Crystallization Mechanisms and Kinetics in Pharmaceutical Systems,” *J. Pharm. Sci.*, **88**, 651-660 (1999) at 657.

Guillory also explains that slurries result in the conversion from a metastable polymorph to a more stable one through a solution phase mediated transformation:

According to McCrone, in a poor solvent the rate of transformation of a metastable to a more stable polymorph is slower. Hence a metastable form once crystallized can be isolated and dried before it is converted to a more stable phase by solution phase mediated transformation.

Guillory at 193 (citing W. C. McCrone, "Polymorphism," Chapter 8 in *Physics and Chemistry of the Organic Solid State*, Vol. II (D. Fox, M. M. Labes, and A. Weissberger, Eds.), Interscience, New York, (1965).

Kiyotaka Sato ("Polymorphic transformations in crystal growth," *J. Phys. D: Appl. Phys.*, 26, B77-B84 (1993) writes:

The driving force of these transformations is the Gibbs energy difference between the polymorphs. Ostwald ripening is a well-known similar phenomenon. It dictates an achievement of a free energy minimum condition in a crystal-medium system consisting of a poly-disperse precipitate, governed by the difference in solubility between the poly-disperse crystal particles [21].

f. A POSA Would Have Been Motivated to Run a Standard Solvent Screen

A POSA also would have been motivated to run a standard polymorph screen using routine solvents and recrystallization conditions with a reasonable expectation of success to form crystalline solids.

In addition to the techniques discussed above, there are a number of standard techniques that scientists use to screen for polymorphs. In his book entitled, "Polymorphism in Molecular Crystals," Bernstein emphasizes the role of solvent screens in finding new polymorphic forms:

One traditional strategy for screening a compound for polymorphic behaviour involves the trial of a variety of solvents and solvent mixtures. Our understanding of the role and choice of solvent has improved considerably and this information, combined with acknowledge of zones of stability can aid in determining crystallization conditions for obtaining metastable form (Threlfall 2000). In addition, there has also been considerable progress in understanding and utilizing the interactions of solvent with the growing crystal (Weissbuch *et al.* 1991; Lahav and Leiserowitz structure determinations of polymorphs with crystal morphological data (*i.e.* crystal habit, and the orientation of molecules projecting from the particular faces exposed) and with known intermolecular interactions between solute molecules and solvent functional groups allows the rational choice of solvent to select a particular polymorphic form (Weissbuch *et al.* 1995). An analysis of this nature was carried out and experimentally confirmed by Blagden *et al.* (1998a, b) for polymorphic modification of sulphathiazole.

Bernstein (2002) at 252.

In his chapter entitled, “Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids” (*Polymorphism in Pharmaceutical Solids*, H. G. Brittain, Ed., 183-226 (1999) at pp. 184-202), Guillory describes a screening protocol that can be used by those in the pharmaceutical industry:

In this context, it is hoped that the following information will prove useful in devising a “screening” protocol for the preparation of the various solid state forms of pharmaceuticals. While one cannot be absolutely certain that no additional forms will be identified in the future, this approach should provide some assurance that “due diligence” has been exercised to isolate and identify crystalline forms that are likely to arise during the normal course of drug development and storage.”

Guillory (1999) at 186.

C. A POSA Would Have Had a Reasonable Expectation of Success in Identifying the Most Stable Polymorphic Form of Sorafenib Tosylate.

The most stable crystalline form of a compound is usually the most readily obtainable form. It would have been routine—and obvious—for a POSA to have obtained the most thermodynamically stable polymorphic form of sorafenib tosylate. For example, a POSA would have used any of the standard techniques to take a melting point of sorafenib tosylate, or their equivalent (DSC, hot bar, TGA, etc) that would have inevitably produced Form 1.

As described above, a POSA would have, for example, slurried sorafenib tosylate in a number of solvents at ambient conditions and would have obtained Form 1 as the most stable polymorph. *See* Bernstein (2002) pp. 27, 255, 297-298.

Therefore, as discussed above, a POSA would have had good reasons to conduct polymorphic screening for sorafenib tosylate (thereby obtaining Polymorph I) and would then have ascertained Polymorph I as the most thermodynamically stable polymorphic form among those generated.

D. The Asserted Claims Would Have Been Obvious

Claims to Polymorph I are obvious because a POSA would have been motivated to run, for example, standard thermal and analytical techniques on any form of sorafenib tosylate, a routine solution-mediated transformation experiment (slurry experiment), or a solvent screen with a reasonable expectation of success to identify the most thermodynamically stable crystalline form of sorafenib tosylate. *See* Guillory (1999) at 191-192; *see also* Byrn (1999) at 274-277. Form 1 was an inevitable result of such slurry experiments.

Also explained above, it was well known in the art that characterization of polymorphs of a solid drug substance was an important aspect of drug development, and a required part of the new drug approval process. *See, e.g.*, Guillory (1999) at 184-185; Byrn (1995) at 945; ICH guidelines at 1, 8. Furthermore, it was well known in the art that the most thermodynamically stable polymorphic form of a drug substance was generally the preferred form for purposes of formulating the drug. *See, e.g.*, Chemburkar (2000) at 413-417; Byrn (1995) at 946-948; Guillory (1999) at 184-186; C. Gu, “Polymorph Screening: Influence of Solvents on the Rate of Solvent-Mediated Polymorphic Transformation,” *J. Pharm. Sci.*, 90, 1878-1889 (2001); S. L. Morissette, “High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids,” *Advanced Drug Delivery Reviews*, 56, 275-300 (2004) at 275-278, 285-291.

Having identified Form 1 as the thermodynamically stable form using routine solvent screens and slurry experiments, a POSA would have been motivated to choose Form 1 as the active pharmaceutical ingredient for development. *See* Guillory at 188-191; Byrn (1995) at 946.

1. Claims 1-4 and 27-31

Claims 1-4 and 27-31 recite sorafenib tosylate Polymorph I and with properties such as specific PXRD reflections, Raman spectroscopy maxima, IR maxima, and melting point. Each of these additional limitations are inherent properties of sorafenib tosylate Polymorph I. Because Polymorph I is obvious, these additional limitations are likewise obvious.

2. Claim 8-10

Claims 8, 9, 10 of '933 patent relate to pharmaceutical formulations comprising sorafenib tosylate Polymorph I. Noted above, it was common to select the most stable polymorph of a compound like sorafenib tosylate for use in a pharmaceutical composition. For example, as taught by Guillory, one of skill in the art would know to employ the thermodynamically stable form a compound during formulation generation. Guillory at 184. See also see November 9, 2015 Notice Letter at 73-74,

Claim 9 depends from claim 8 and includes the further limitation of including inert, nontoxic, pharmaceutically suitable excipients in the composition. Numerous prior art references, including U.S. Patent App. Pub. No. 2003/0232765 to Carter et al. ("Carter"), disclose the use of such excipients, as described in the November 9, 2015 Notice Letter. November 9, 2015 Notice Letter at 72-73, 106; Carter at ¶ 65. Similarly, U.S. Patent App. Pub. US 2003/0207870 to Dumas et al. ('870 Publication) discloses the use of such excipients together with sorafenib.

Claim 10 depends from claim 8 and specifies that the sorafenib tosylate present in the composition be at least 90% (by weight) sorafenib tosylate Polymorph I. BAY_NEXAVAR_00102008.

Accordingly, claims 8-10 are invalid as obvious.

3. Claims 16-21

Claim 16 relates to administering a therapeutically effective amount of sorafenib tosylate Polymorph I. Because sorafenib tosylate was a known active pharmaceutical composition, it would have been obvious to administer an effective amount to treat some condition. *See e.g.*, Carter at ¶¶ 36, 45; *see also* '870 Publication. Combined with the reasons articulated above for claim 1, claim 17 is invalid.

Claim 17 depends from claim 16 and specifies that the disorder is abnormal angiogenesis, hyperpermeability processes, bone marrow diseases, carcinoma and carcinogenic cell growth. Carter teaches the treatment of various cancers, including pancreatic, lung, colon,

ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. Carter at ¶¶ 36, 45; *see also* 870 Publication. Combined with the reasons articulated above for claim 1, claim 17 is invalid as obvious.

Claim 18 depends from claim 16 and specifies that the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid, kidney, or intestine. Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. Carter at ¶¶ 36, 45; '870 Publication. Thus, claim 18 is invalid as obvious.

Claim 19 recites a method for treating a disorder, comprising administering a therapeutically effective amount of the compositions of any one of claims 8 to 15. For the same reasons articulated for claims 8 to 10 and claims 16, claim 19 is invalid as obvious.

Claim 20 depends from claim 19 and specifies that the disorder is abnormal angiogenesis, hyperpermeability processes, bone marrow diseases, carcinoma and carcinogenic cell growth. Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. Carter at ¶¶ 36, 45. Combined with the reasons articulated above for claim 1, 17 and 19, claim 20 is invalid as obvious.

Claim 21 depends from claim 19 and specifies that the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid, kidney, or intestine. Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. Carter at ¶¶ 36, 45. Combined with the reasons articulated above for claim 1, 17 and 19, and 20, Claim 21 is invalid as obvious.

E. Obviousness-type Double Patenting

The '933 patent also is invalid for obviousness-type double patenting over U.S. Patents No. 7,351,834 ("the '834 patent") and 8,618,141 ("the '141 patent"), both of which are commonly owned, licensed or assigned with the '933 patent and expire before it.

The '834 patent issued April 1, 2008. It expires January 12, 2020, according to the Orange Book. Each of the asserted claims of the '933 patent is invalid for obviousness-type double patenting over at least claim 41 of the '834 patent. Claim 41 is directed to: "A compound of claim 39 which is a tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea."

The '141 patent issued December 31, 2013. It expires February 11, 2023, according to the Orange Book. Each of the asserted claims of the '933 patent is invalid for obviousness-type double patenting over at least claim 6 of the '141 patent. Claim 6 is directed to:

A method of blocking tumor angiogenesis in a human or other mammal comprising administering to a human or other mammal with a tumor of the breast, gastrointestinal tract, kidney, ovary or cervix, an effective amount of the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N-ethylangiomethylcarbamoyl-4-pyridyloxy)phenyl)urea tosylate

Each of the asserted claims is an obvious variant of the subject matter of the claims of the '834 and '141 patents for the reasons set out above.

INTERROGATORY NO. 4:

Other than as set forth in your responses to Interrogatory Nos. 1-3, is there any other basis on which you contend that the Court should not find that the manufacture, use, offer for sale, sale, or importation of Mylan's ANDA Product would infringe at least one valid and enforceable claim of the patents-in-suit or that you are not liable for inducing the infringement of one or more claims of the patents-in-suit? If your answer is anything other than an unequivocal "no," state all bases for your contention and identify for each challenged claim all facts, documents, and circumstances on which you rely for your contention.

RESPONSE TO INTERROGATORY NO. 5:

Mylan incorporates the General Objections set forth above. Mylan objects to this interrogatory as overly broad, unduly burdensome, and oppressive to the extent it seeks information that is irrelevant to the claims and defenses at issue in this case and is not proportional to the needs of the case. For example, Mylan objects to the phrase "any other basis," "all bases," and "all facts, documents, and circumstances" as being overly broad and

requiring the production of trivial documents and other documents with limited, if any, relevance to the parties' claims or defenses. Mylan further objects to the phrases "at least one valid and enforceable claim," "one or more claims," and "each challenged claim" to the extent that this interrogatory seeks information not relevant to the asserted claims. Mylan will be responding to this interrogatory only insofar as it is relevant to the claims currently asserted by Plaintiffs. Mylan objects to this interrogatory to the extent it calls for a legal conclusion. Mylan further objects to this interrogatory as premature under the Scheduling Order, as discovery is just beginning, Mylan has not received any discovery from Bayer, and no depositions have been conducted. Mylan further objects to this interrogatory as premature under the Local Rules and the Default Standard for Discovery Including Discovery of ESI, which requires Plaintiffs to produce initial claim charts demonstrating how each product allegedly infringes each asserted patent claim before Defendants provide any initial contentions. This interrogatory essentially requires Mylan to provide non-infringement contentions before Plaintiffs have provided its infringement contentions. Mylan further objects to this interrogatory to the extent that Mylan does not bear the burden of proof regarding infringement, including induced infringement. Mylan further objects to this interrogatory as seeking expert discovery prior to the dates for expert reports. Mylan objects to this interrogatory to the extent it seeks information that is confidential, protected by the right of privacy, and/or protected from disclosure by applicable privileges and protections, including without limitation the attorney-client privilege, work product protection, common interest privilege and/or consulting expert privilege. Mylan objects to this interrogatory to the extent it seeks information the disclosure of which is subject to third-party confidentiality obligations or a protective order. Mylan objects to this interrogatory to the extent it requests information not in Mylan's possession, custody, or control. Mylan objects to this interrogatory to the extent it calls for information already in Plaintiffs' possession, or calls for publicly available information. Mylan objects to this interrogatory as vague and ambiguous as to the term "circumstances." Mylan proposes that the parties meet and confer to determine a meaning.

Mylan objects to this interrogatory to the extent it includes multiple subparts, each of which constitutes a separate Interrogatory pursuant to Fed. R. Civ. P. 33(a)(1). Mylan further objects to this interrogatory as improper under Fed. R. Civ. P. 33(a) because it purports to be a single interrogatory but contains multiple subparts. This interrogatory has at least two discrete subparts and is, therefore, at least two interrogatories. Mylan further objects to the description of this interrogatory as Interrogatory No. 4. Mylan considers this Request to be Interrogatory Nos. 15-16.

Subject to and without waiving the foregoing objections, and to the extent understood, Mylan responds that it is Plaintiffs' burden to provide initial infringement contentions under the Scheduling Order because infringement is their burden. Mylan will supplement its response after Plaintiffs provide appropriate infringement contentions.

Discovery is on-going and Mylan will supplement its response if necessary and in accordance with the Federal Rules of Civil Procedure. Mylan is available to meet and confer with Plaintiffs to determine an appropriate discovery schedule for the provision of information, documents, and things in accordance with the Scheduling Order, Local Rules for the District of Delaware, the Default Standard for Discovery Including Discovery of ESI, and the Federal Rules of Civil Procedure.

INTERROGATORY NO. 5:

Identify all individuals involved in the decision to develop Mylan's ANDA Product and the date on which Mylan decided to proceed with the development of Mylan's ANDA Product.

RESPONSE TO INTERROGATORY NO. 6:

Mylan incorporates the General Objections set forth above. Mylan objects to this interrogatory as overly broad, unduly burdensome, and oppressive to the extent it seeks information that is irrelevant to the claims and defenses at issue in this case and is not proportional to the needs of the case. For example, Mylan objects to the phrase "all individuals" as being overly broad and requiring the production of trivial documents and other documents with limited, if any, relevance to the parties' claims or defenses. Mylan objects to

this interrogatory to the extent it seeks information that is confidential, protected by the right of privacy, and/or protected from disclosure by applicable privileges and protections, including without limitation the attorney-client privilege, work product protection, common interest privilege and/or consulting expert privilege. Mylan objects to this interrogatory to the extent it seeks information the disclosure of which is subject to third-party confidentiality obligations or a protective order. Mylan objects to this interrogatory to the extent it requests information not in Mylan's possession, custody, or control. Mylan further objects to this interrogatory as premature under the Scheduling Order, as discovery is just beginning. Mylan objects to this interrogatory as vague and ambiguous as to the phrases "involved in the decision" and "decided to proceed with the development." Mylan proposes that the parties meet and confer to determine a meaning. Mylan objects to this interrogatory to the extent it includes multiple subparts, each of which constitutes a separate Interrogatory pursuant to Fed. R. Civ. P. 33(a)(1). Mylan further objects to this interrogatory as improper under Fed. R. Civ. P. 33(a) because it purports to be a single interrogatory but contains multiple subparts. This interrogatory has at least two discrete subparts and is, therefore, at least two interrogatories. Mylan further objects to the description of this interrogatory as Interrogatory No. 5. Mylan considers this Request to be Interrogatory Nos. 17-18.

Subject to and without waiving the foregoing objections, and to the extent understood, Mylan responds as follows: pursuant to Rule 33(d) of the Federal Rules of Civil Procedure, Mylan states that it has no information responsive to this interrogatory because Mylan did not develop the ANDA Product.

Discovery is on-going and Mylan will supplement its response if necessary and in accordance with the Federal Rules of Civil Procedure.

OF COUNSEL:

Douglas H. Carsten
Nellie J. Amjadi
WILSON SONSINI GOODRICH & ROSATI
12235 El Camino Real, Suite 200
San Diego, CA 92130
Tel: (858) 350-2300

Dennis D. Gregory
WILSON SONSINI GOODRICH & ROSATI
1301 Avenue of the Americas, 40th Floor
New York, NY 10019-6022
Tel: (212) 999-5800

Nancy L. Zhang
WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304
Tel: (858) 350-2300

Dated: August 10, 2016
1231119 / 42284 (cons.)

POTTER ANDERSON & CORROON LLP

By: /s/ Bindu A. Palapura
Richard L. Horwitz (#2246)
David E. Moore (#3983)
Bindu A. Palapura (#5370)
Stephanie E. O'Byrne (#4446)
Hercules Plaza, 6th Floor
1313 N. Market Street
Wilmington, DE 19801
Tel: (302) 984-6000
rhorwitz@potteranderson.com
dmoore@potteranderson.com
bpalapura@potteranderson.com
sobyne@potteranderson.com

*Attorneys for Defendant Mylan
Pharmaceuticals Inc.*

CERTIFICATE OF SERVICE

I, Bindu A. Palapura, hereby certify that on August 10, 2016, true and correct copies of the within document were served on the following counsel of record at the addresses and in the manner indicated:

VIA ELECTRONIC MAIL

Jack Blumenfeld
Maryellen Noreika
Derek J. Fahnestock
Morris, Nichols, Arsht & Tunnel LLP
1201 North Market Street
P. O. Box 1347
Wilmington, DE 19899
jblumenfeld@mnat.com
mnoreika@mnat.com
dfahnestock@mnat.com

Bruce R. Genderson
Adam L. Perlman
Dov P. Grossman
Jessica Rydstrom
Joelle Perry
Teagan J. Gregory
Christopher S. Geyer
Williams & Connolly LLP
725 Twelfth Street, N.W.
Washington, DC 20005
bgenderson@wc.com
aperlman@wc.com
dgrossman@wc.com
jrydstrom@wc.com
jperry@wc.com
tgregory@wc.com
cgeyer@wc.com

/s/ Bindu A. Palapura

Bindu A. Palapura

EXHIBIT 3

REDACTED
IN ITS
ENTIRETY

EXHIBIT 4

D36

- 1 -

Affidavit

Being aware of the importance of an affidavit as a means of credible evidence of actual facts in a well-ordered procedure before the European Patent Office (EPO), I, Dr Alfons Grunenberg, born on 30 July 1954 in Wanne-Eickel, resident in Bismarckstraße 87, 42115 Wuppertal, Germany, declare the following for submission with the EPO in the opposition proceedings against the European patent EP 1 797 038 B1 (patent):

I, Dr Alfons Grunenberg, received a diploma in chemistry from the University of Essen in 1983. I was awarded my PhD in Chemistry from the University of Essen in 1986. I started working with Bayer in 1986 and until my retirement in 2011, I primarily worked on crystal modifications and polymorphism of organic compounds and thermal analysis. A more detailed curriculum vitae is enclosed herewith (Enclosure 1). I have been summoned by the Opposition Division on 29 January 2016 and will testify as a witness during the Oral Proceedings of EP'038 on 12 July 2016.

Starting in 1999, I investigated the polymorphic behavior of sorafenib tosylate.

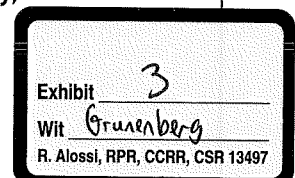
In July 1999, I obtained a first sample of sorafenib tosylate (505063) together with its manufacturing protocol (Enclosure 2), which is identical to the manufacturing protocol described in Example 1 of the patent. I supervised the DSC (differential scanning calorimetry) analysis of this sample (Enclosure 3). Two endothermal peaks were identified in the DSC diagram. A first minor endothermal peak was identified at an onset temperature of 178 °C, which shows a solid-solid phase transition. A second major endothermal peak at an onset temperature of 219 °C indicates the melting of sorafenib tosylate.

An XRD (X-ray diffractogram) was not recorded with the first sample 505063.

In November 1999, I obtained a second sample 505158 from an up-scaling trial for producing sorafenib tosylate, the manufacturing protocol of which is enclosed as Enclosure 4. I supervised the DSC analysis (Enclosure 5) and XRD measurements (Enclosure 6) of the second sample.

The DSC analysis of the second sample (Enclosure 5) displays two peaks, one minor endothermal peak at an onset temperature of 194 °C and one major endothermal melting peak at an onset temperature of 226 °C.

The X-ray diffractogram of the second sample (Enclosure 6) corresponds to the X-ray diffraction patterns of polymorph II in Figure 2 of the patent. Particularly, the



MYL_SOR00012607

- 2 -

three intense peaks at $2\theta = 7.3^\circ$, 8.8° and 10.5° unambiguously identify the second sample as polymorph II as defined in the patent.

In December 1999, I obtained a third sample of sorafenib tosylate (527319H), which was obtained by micronizing the second sample (505158). The micronization procedure is described in Enclosure 7. I supervised the DSC analysis (Enclosure 8) of the third sample.

The DSC analysis of the third sample (Enclosure 8) displays two peaks, one minor endothermal peak at an onset temperature of 188°C and one major endothermal melting peak at an onset temperature of 222°C .

I was told that the retained sample of 527319H was subjected to an XRD re-analysis instructed by Dr Britta Olenik in April 2013, which was introduced as evidence in the opposition proceedings as D27.

The X-ray diffractogram of the third sample (D27) corresponds to the X-ray diffraction patterns of polymorph II in Figure 2 of the patent. Particularly, the three intense peaks at $2\theta = 7.3^\circ$, 8.8° and 10.5° unambiguously identify the second sample as polymorph II.

Conclusion

Each of the three sorafenib tosylate samples shows two peaks in their DSC diagram (Enclosures 3, 5 and 8), one minor endothermal peak, the onset temperature of which is between 178 - 194°C , and one major peak, the onset temperature of which is between 219 - 226°C . The DSC analysis of all samples shows the characteristic DSC pattern of polymorph II according to Figure 1 in the patent, including one minor and one major endothermal peak. The slight shift in the onset temperatures can be explained by common kinetic effects and also depends on the particle size and purity of the sample. The presence of the minor endothermal peak is clear evidence that the samples are not in the modification of polymorph I but in the modification of polymorph II (see Figure 1 in the patent).

Furthermore, it is also confirmed by the DSC data that said samples are not in the modification III. The DSC pattern of polymorph III is characterized by two endothermal peaks, including a minor peak and a major peak, and in addition an exothermal peak close behind to the minor endothermal peak. The characteristic exothermal peak is absent in polymorph II.

The uniform DSC patterns of samples 505063, 505158 and 527319H can only be assigned to polymorph II as defined in the patent (Figure 1). The additional X-ray diffractograms, which are identical to the XRD pattern of polymorph II in the patent

- 3 -

(Figure 2), unambiguously identify the samples as polymorph II. Consequently, all samples (505063, 505158, and 527319H) are present in the modification of polymorph II.

The results show that the manufacturing process of sorafenib tosylate according to sample 505063 (Enclosure 2), which is identical to the manufacturing protocol described in Example 1 of the patent, and according to the second sample 505158 (Enclosure 4) reproducibly resulted in the modification of polymorph II.

Wuppertal, 2016, April 20

Alfons Grunenberg
Dr Alfons Grunenberg

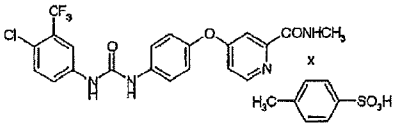
Encls
Enclosures 1-8

Enclosure 1

Lebenslauf Dr. Alfons Grunenberg

geb. am	30.07.1954
in:	Wanne-Eickel
Schulbesuch:	1961 – 1966 Volksschule in Wanne-Eickel 1966 – 1971 Realschule in Wanne-Eickel 1974 – 1976 Fachoberschule für Technik Bochum 1976 – 1986 Chemie-Studium an der GHS Essen Abschluss Diplom – 24.06.1983 Promotion – 23.01.1986
Werdegang:	1971 – 1974 Ausbildung zum Chemielaboranten Bayer AG Leverkusen 1974 1 Monat Chemielaborant Bayer AG 1974 – 1975 Zivildienst 1983 – 03/1986 Doktorand GHS Essen 01.04.1986 Eintritt Bayer AG Pflanzenschutz Dormagen (PF-P / FVL) Laborleitung 01.12.1989 Versetzung nach Wuppertal Pharma-QA Entwicklung Laborleitung Aufbau Labor Polymorphieanalytik 01.05.1997 Ernennung zum Leitenden Angestellten 31.10.2011 Austritt

Enclosure 2

Thema : Bay 54-9085	Datum : 8.06.99
Tosylat	Nr.: MMG 2519-6
Art.-Nr.: 05381339	Pt.-Nr.: 505063
Zweck des Versuches :	Sonstiges :
GLP-Ansatz	1237,4g = 100%
Formel :  $C_{21}H_{18}ClF_3N_4O_3 \times C_7H_4O_3S$ 638,6 g/mol	
Ergebnis : 1129,6g = 91,3% d. Theorie	
Einsatzmengen: 367,4 g (0,791 mol) MMG 2507-9(Bay 43-9006) 406,3 g (0,875 mol) MMG 2507-10(Bay 43-9006) 129,3 g (0,278 mol) MMG 2507-11(Bay 43-9006) 2700 ml Ethanol ZTL: 06.07.99 451,7 g (2,377 mol) MMG 2520-2 (p-Toluolsulfonsäure) 1340 ml Ethanol ZTL: 06.07.99 3 x 830 ml Ethanol ZTL: 06.07.99	
Arbeitsweise: 903g MOS 2507-9,10,11 in 2700ml Ethanol vorgelegt.	
451,7g MMG 2520-2 in 1340ml Ethanol gelöst und bei RT zugetropft .	
1h bei RT gerührt..	
Abgesaugt und dreimal mit je 830ml Ethanol gewaschen.	
Im Vakuum bei 50°C, Beiluft, getrocknet.	
Auswaage: 1129,6g	
Die 1129,6g in zwei 1000mlBraunglasweithalsflaschen gefüllt.	

Bayer Elberfeld

PH-OP-Elb-CE-VE1-Labor1

Labor : Dr. Müller-Glennemann

Bearbeiter :

Schmitt

MYL_SOR00012611

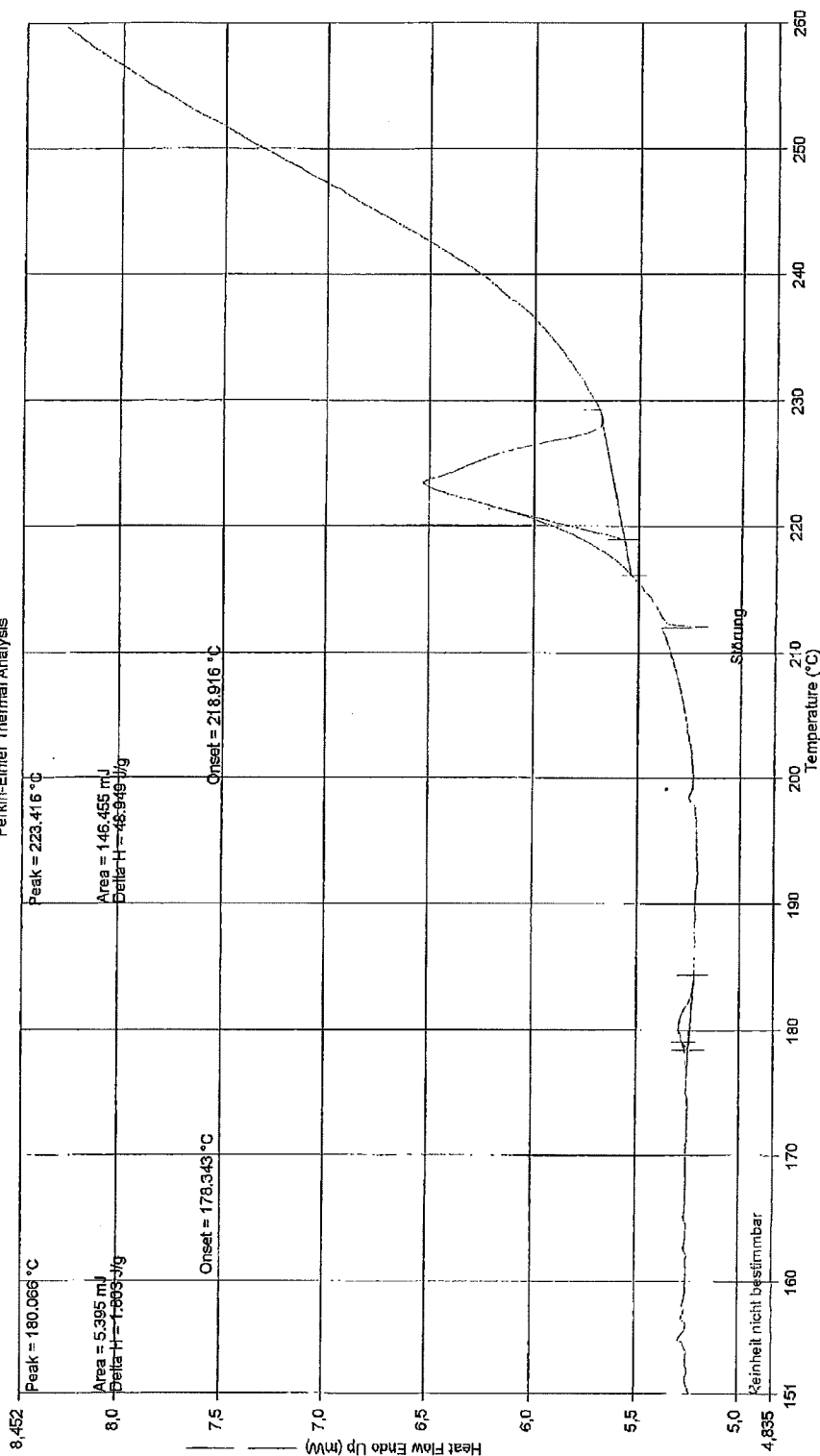
Enclosure 3

Filename: C:\PEIDSC7-Robotik\dr12132.dsc
 Data Collected: 23.07.99 12:58:35
 Baseline Filename: C:\PEIDSC7-Robotik\bases.dsc
 Operator ID: Mlze
 Sample ID: Bay 54-9085 PL505063 Dr. Weinz
 Sample Weight: 2.992 mg
 Comment: DSC7Rob.11860/AM-AA1572-03S-180/181/
 N2-StromVAL-Tiegel, perforiert, SET 23.07.99

Bay 54-9085 PL505063 Dr. Weinz dr12132.dsc
 Heat Flow Endo Up (mW) : Step: 1

23.07.99

Perkin-Elmer Thermal Analysis



23.07.99 13:30:09

1) Heat from 150.00 °C to 260.00 °C at 2.00 °C/min

23.7.99

MYL_SOR00012612

Enclosure 4

Dr. Lögers
PH-OP-ELB-CE-VE, GMP-Labor Geb.70

Pt.Nr.

505158

Ans.Nr.:

Seite 2 von 21

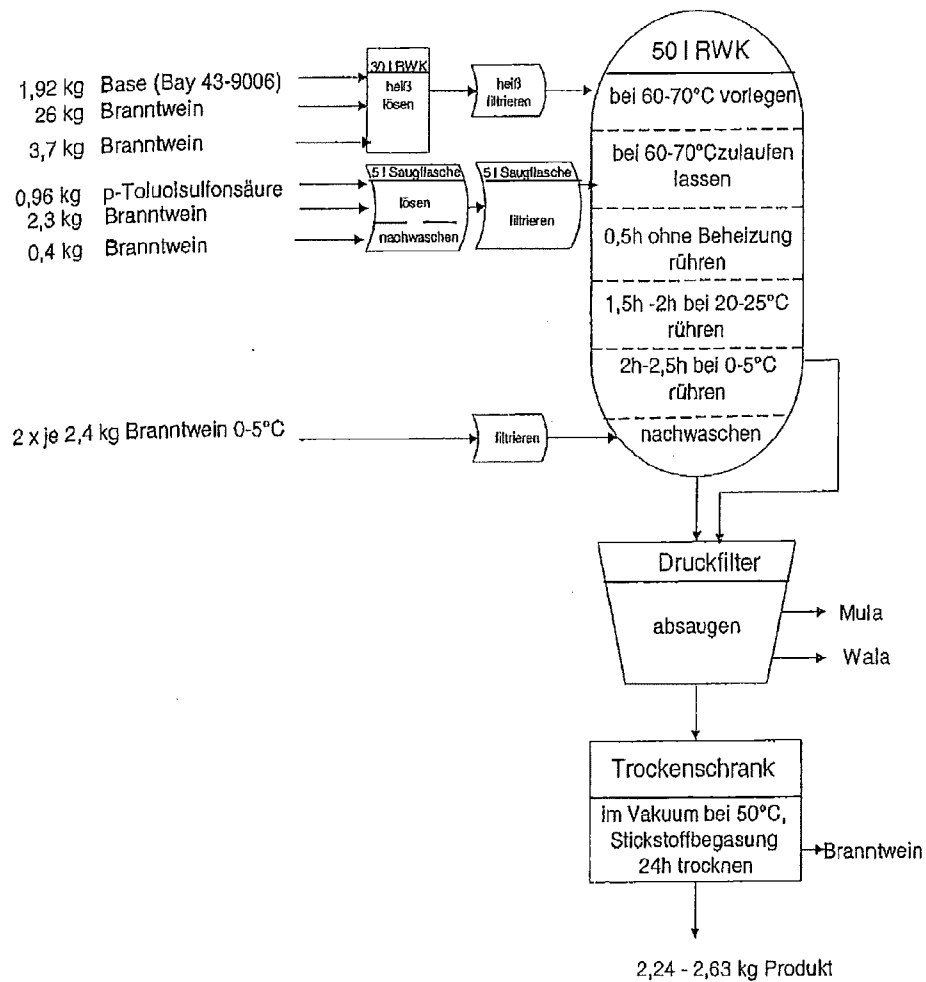
L 1/99

Projekt: Bay 54-9085

Stufe: Bay 54-9085

Verfahren: Tosylierung

Blockfließbild

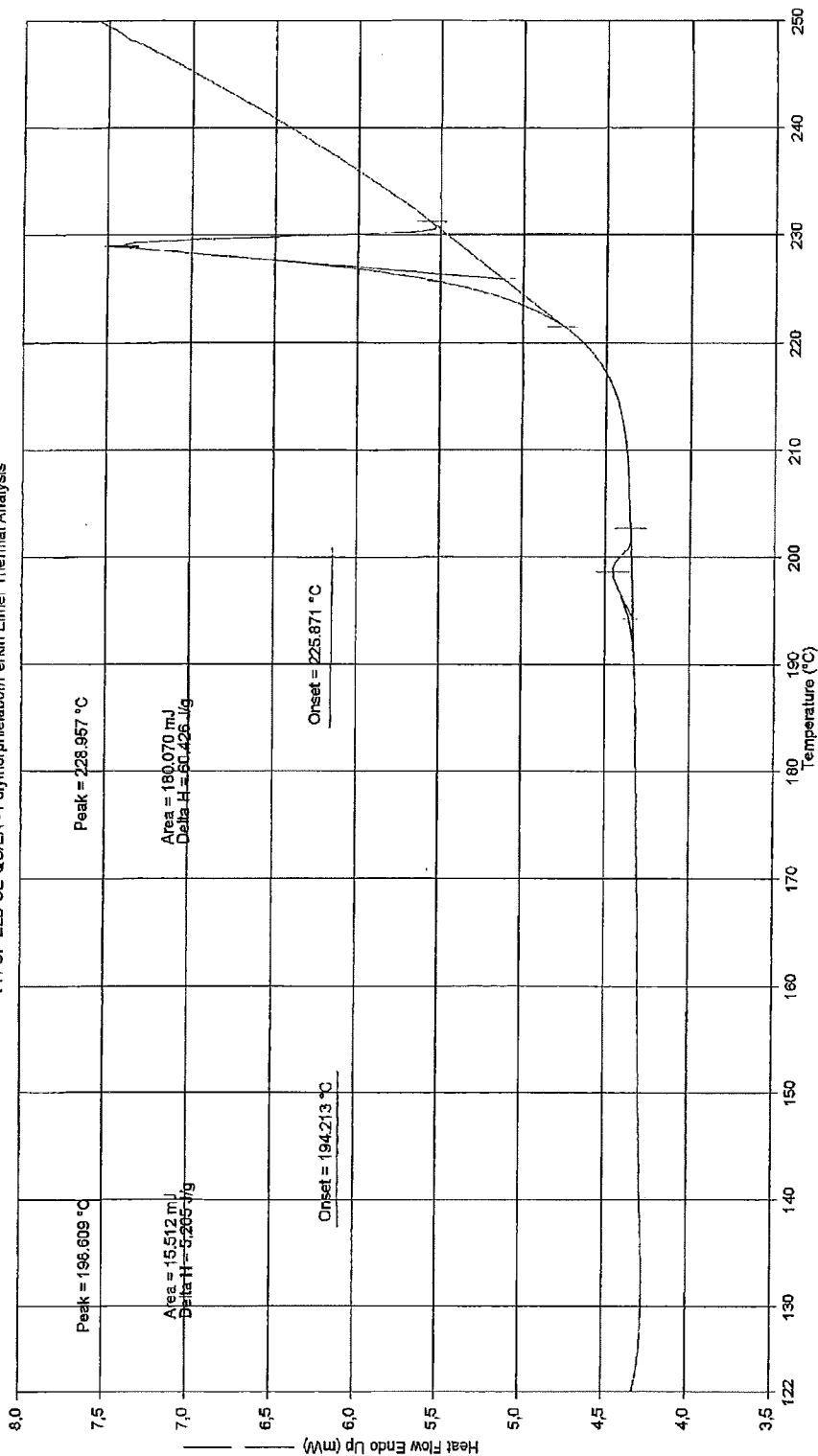


Bemerkungen: (Hier sind Abweichungen und besondere Beobachtungen zu den einzelnen Punkten einzutragen)

Enclosure 5

Filename: C:\PE\Pyris\Data\pyr2333.dod
 Data Collected: 30.11.99 12:04:47
 Baseline Filename: C:\PE\Pyris\Data\Baseline 102.dod
 Operator ID: Engels
 Sample ID: Bay 54-9085/ 5051/58/ Spekt.
 Sample Weight: 2.980 mg
 Comment: DSC-Pyris1(155239):AM-AAL57;2-035-180/181
 N2-Ström;AL-Tiegel perforiert;SET:29,11,99

PH-OP-ELB-CE-QC/EA - Polymorphielabor/Perkin Elmer Thermal Analysis



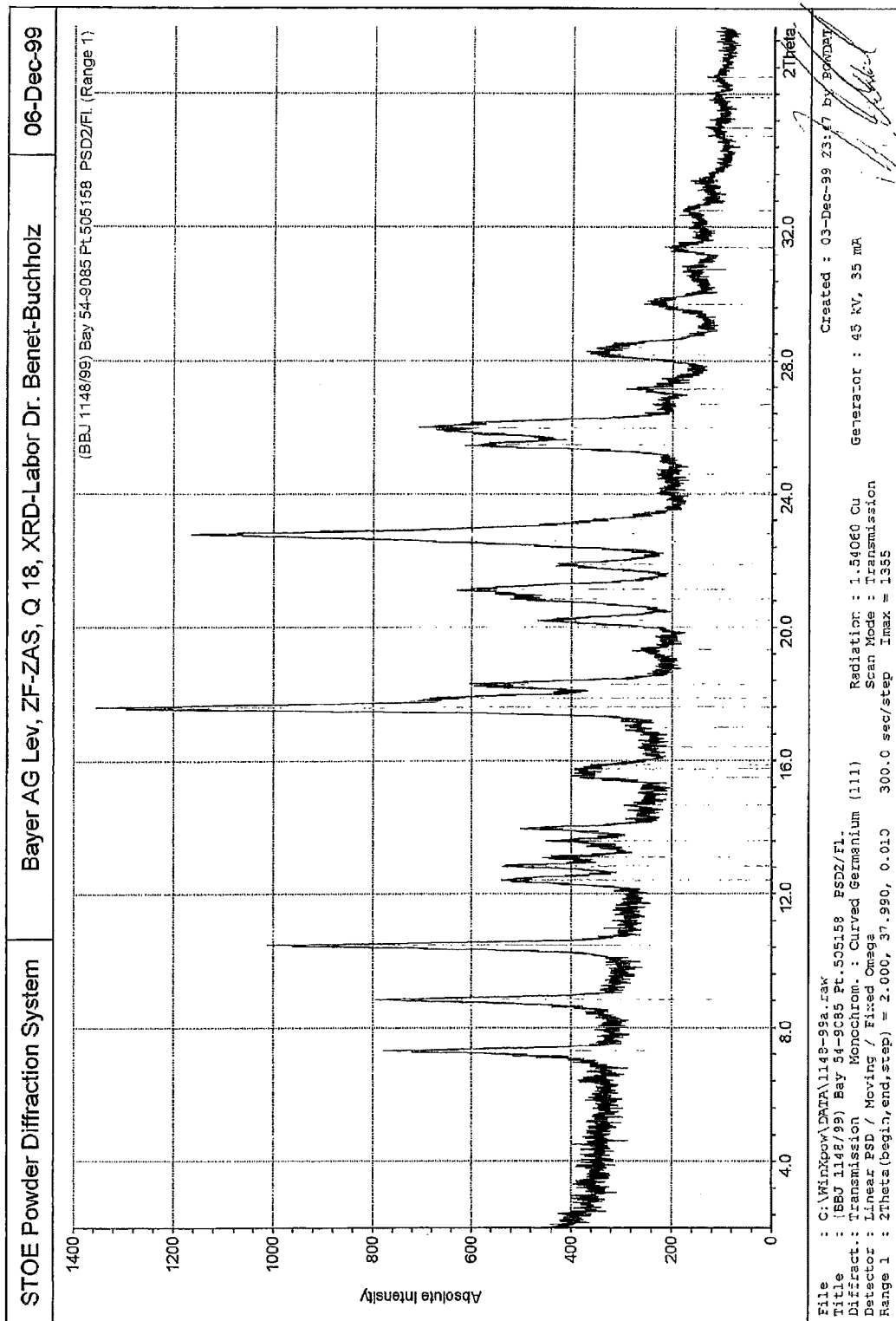
30.11.99 12:12:02

1) Heat from 120.00°C to 250.00°C at 2.00°C/min

30.77.99

MYL_SOR00012614

Enclosure 6



MYL_SOR00012615

2,37 / 07.12.99
Auftragsgröße: ~~60,0~~ kg
Order size: 60.0 kg

[illegible]

Berechnung auf den Seiten: 1/3/4/11
überprüft. 07.12.99 luo

Kopie stimmt mit dem Original überein

3. JAN. 2000

PH-OP-ELB-GE-QC/EA
Freigeabestelle

MYL SOR00012616

BAYER AG PH-PD PCS	Herstellprotokoll Batch Manufacturing Record Seite 2	VM 01, Ausgabe 01
Material-Nr. Product No. 00 05407052	Materialbezeichnung Product name BAY 54-9085 MICRONIZED	Charge 527319 PART 1
Besondere Hinweise: Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske P3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen. Special notes: Use rubber gloves, safety glasses, ear protectors and dust mask P3. Water dangerous, must not get in the sewage. Protect from light.		

Anweisung für die Herstellung: Instructions for manufacture: Einwaage Einsatzstoffe Weighing of ingredients Mahlen in der LSM-100 Mill on the LSM-100 IPC-Korngrößenverteilung IPC-Particle size distribution Ausbeutebestimmung Yield determination	An der Fertigung beteiligte Personen Staff involved in manufacturing <table> <thead> <tr> <th>Name Name (Blockchrift) (Capital letters)</th> <th>Zeichen Initials</th> </tr> </thead> <tbody> <tr> <td>JANETZKY</td> <td>JD</td> </tr> <tr> <td>Kohlmeier</td> <td>UK</td> </tr> </tbody> </table>	Name Name (Blockchrift) (Capital letters)	Zeichen Initials	JANETZKY	JD	Kohlmeier	UK
Name Name (Blockchrift) (Capital letters)	Zeichen Initials						
JANETZKY	JD						
Kohlmeier	UK						
Schutzmaßnahmen: Special notes: Lagerhinweise: Notes for storage:	Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske P3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen. Die Sicherheitsdatenblätter und/oder Betriebsanweisungen für alle Produktionsschritte werden dem HP-Schein vor Beginn der Fertigung in Kopien beigelegt. Use rubber gloves, safety glasses, ear protectors and dust mask P3. Water dangerous, must not get in the sewage. Protect from light. Append copies of the safety data sheets and/or the operating instructions for all production steps to the Batch Manufacturing Record before the start of production. Vor Feuchtigkeit schützen. Protect from moisture. Vor Licht schützen. Protect from light.						
Reinigungsverfahren: Cleaning procedure:	Es gilt das Standardreinigungsverfahren. Standard cleaning procedure applicable. Zusätzlich sind die produktberührenden Oberflächen mit Ethanol nachzureinigen. Additional clean-all surfaces which come into contact with the product with ethanol. IPC- Tensidprüfungen gemäß 1-300-153 durchführen. Carry out IPC-Surfactant testing according to AM 1-300-153.						

BAYER AG / PH-PD PCS		Herste. Protokoll Batch Manufacturing Record		Seite 3		VM 01, Ausgabe 01	
Material-Nr. Product No. 00 05407052		Materialbezeichnung Product name BAY 54-9085 MICRONIZED				Charge 027319 H .PART.	
Besondere Hinweise: Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske P3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen. Special notes: Use rubber gloves, safety glasses, ear protectors and dust mask P3. Water dangerous, must not get in the sewage. Protect from light.							

Einwaageblatt für die Mahlung:
Weighing sheet for milling:

Rezepturstückliste Ingredient list										
ID	Material-Nr. Article no.	Materialbezeichnung Product name	Charge Batch no.	MSO	Menge theor. Theor. amount	Menge Ans. Amount for use	Istmenge Actual amount	Waage Balance	Zeichen Init.	Datum Date
E1	00 05381339	BAY 54-9085	505153	kg	2,37 / 15.01.12.99 -66,6	—	XXXXXXX	XXXXXX	XXXXXX	XXXXXX
E1	00 05381339	Brutto vor Entnahme	XXXXXXX	kg	dok.	—	4,1840	3	UK	8.12.99
E1	00 05381339	- Brutto nach Entnahme	XXXXXXX	kg	dok.	—	1,2091	3	UK	9.12.99
E1	00 05381339	= Netto Entnahme (Anliefergebinde 1)	XXXXXXX	kg	dok.	—	2,3749	XXXXXX	XXXXXX	9.12.99
E1	00 05381339	BAY 54-9085	505153	kg	2,37 / 15.01.12.99 -66,6	XXXXXXX	XXXXXXX	XXXXXX	XXXXXX	XXXXXX
E1	00 05381339	Brutto vor Entnahme	XXXXXXX	kg	dok.	—	9.12.99	XXXXXX	XXXXXX	XXXXXX
E1	00 05381339	- Brutto nach Entnahme	XXXXXXX	kg	dok.	—	—	XXXXXX	XXXXXX	XXXXXX
E1	00 05381339	= Netto Entnahme (Anliefergebinde 2)	XXXXXXX	kg	dok.	—	—	XXXXXX	XXXXXX	XXXXXX

Druckdruck: 27.10.99

MYL_SOR00012618

BAYER AG / PH-PD PCS		Herstellprotokoll Batch Manufacturing Record		Seite 4	VM 01, Ausgabe 01	
Material-Nr. Product No. 00 05407052		Materialbezeichnung Product name BAY 54-9085 MICRONIZED		Charge 52731911 .PART.		

Besondere Hinweise: Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske P3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen.

Special notes: Use rubber gloves, ear protectors and dust mask P3. Water dangerous, must not get in the sewage. Protect from light.

Einwaageblatt für die Mahlung:
Weighing sheet for milling:

Rezepturstückliste Ingredients list											
ID	Material-Nr. Article no.	Materialbezeichnung Product name	Charge Batches	MSO	Menge theor. Theor. amount	Menge Ans. Amount for use	Istmenge Actual amount	Waage Balance	Zeichen Init.	Zeichen Falt.	Datum Date
E1	00 05381339	BAY 54-9085		kg	2,37 / 16.01.1999 -60-0-	XXXXXXXXXX	XXXXXXXXXX	XXXXXX	XXXXXX	XXXXXX	XXXXXX
E1	00 05381339	Brutto vor Entnahme	XXXXXXXXXX	kg	dok.						
E1	00 05381339	- Brutto nach Entnahme	XXXXXXXXXX	kg	dok.						
E1	00 05381339	= Netto Entnahme (Anliefergebinde 3)	XXXXXXXXXX	kg	dok.		9.12.99	XXXXXX		XXXXXX	
E1	00 05381339	BAY 54-9085		kg	2,37 / 16.01.1999 -60-0-	XXXXXXXXXX	XXXXXXXXXX	XXXXXX	XXXXXX	XXXXXX	XXXXXX
E1	00 05381339	Brutto vor Entnahme	XXXXXXXXXX	kg	dok.						
E1	00 05381339	- Brutto nach Entnahme	XXXXXXXXXX	kg	dok.						
E1	00 05381339	= Netto Entnahme (Anliefergebinde 4)	XXXXXXXXXX	kg	dok.			XXXXXX		XXXXXX	

MYL_SOR00012619

BAYER AG PH-PD PCS	Herstellprotokoll Batch Manufacturing Record Seite 5	VM 01, Ausgabe 01
Material-Nr. Product No. 00 05407052	Materialbezeichnung Product name BAY 54-9085 MICRONIZED	Charge 527315 PART 1
Besondere Hinweise: Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske P3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen. Special notes: Use rubber gloves, safety glasses, ear protectors and dust mask P3. Water dangerous, must not get in the sewage. Protect from light.		

Mahlen in der Luftstrahlmühle

Betriebsmittelkontrolle
Production equipment check

Raum: 244
Room:

LSM-100. Hier bitte Reinigungsetikett oder bei fliegendem Chargeumschmel Geräteeikett der Vorgängercharge einkleben bzw. Vorgängercharge hier in dem Gerät zuletzt einer von mehreren

Al PH - PD - PCS Klinikmusterherstellung
VM 01, Ausgabe 01

Geräteeikett für LSM 100

Materialbez. : BAY 54-9085 MICRONIZED
Material-Nr. : 00 05407052
Chargen-Nr. : PART

Ansatz: 1 von: 1

Datum: 8. 12. 99

Blatt 4 von 24

Für die anlaufende Fertigung nicht benötigte Produkte, Unterlagen oder Materialien sind entfernt worden.

Die Ausrüstung und der Raum sind sauber und betriebsbereit.

Products, documents or materials not required for the current production run have been removed.
The equipment and the room are clean and ready for production.

Datum:
Date:


8. 12. 99

Ausführender:
Carried out by:

70

BAYER AG PH-PD PCS	Herstellprotokoll Batch Manufacturing Record Seite 6	VM 01, Ausgabe 01
Material-Nr. Product No. 00 05407052	Materialbezeichnung Product name BAY 54-9085 MICRONIZED	Charge 527318 PART H
Besondere Hinweise: Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske P3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen. Special notes: Use rubber gloves, safety glasses, ear protectors and dust mask P3. Water dangerous, must not get in the sewage. Protect from light.		

Anweisung

Mahlparameter zu Beginn eines jeden Fertigungstages und bei jedem Produktgebinde- wechsel dokumentieren. Record the milling parameters at the start of each day of manufacture and each time a product container is changed. - im Laufe der Mikronisierung Mahlkammer auf Anbackungen überprüfen, ggf. zwischenreinigen - watch for caking in the milling chamber during the process, clean intermediately if necessary Erstes Anzeichen dafür, daß sich die Mahlkammer zusetzt, ist die Tatsache, daß der Produktdurchsatz reduziert werden muß. A first sign for a build-up of material in the milling chamber is the fact that the feeding rate has to be reduced - Zwischenreinigung durch ein „ZR“ in der Zeile „Gebinde“ dokumentieren - record intermediate cleaning by notifying a „ZR“ in the line „bin“
Datum: 8.12.99 Ausführer:  Date: Carried out by:

BAYER AG / PH-PD PCS		Herstell.-protokoll Batch Manufacturing Record		Seite 7	VM 01, Ausgabe 01
Material-Nr. Product No.		Materialbezeichnung Product name		Charge	
00 05407052		BAY 54-9085 MICROWIZED		1.2.12.49 H .PART.	
Besondere Hinweise: Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske p3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen. Special notes: Use rubber gloves, safety glasses, ear protectors and dust mask p3. Water dangerous. Must not get in the sewage. Protect from light.					


Mahlen in der Luftstrahlmühle (Mahlhammer: Teflon)						
Gerät: LSM-100 Apparatus: LSM-100						
Parameter	Einheit Units	Richtwert Reference value	Sollwert Required value	Datum Date	Gebinde Bin	
Injektorluft (Stickstoff) Injector air (nitrogen)	bar	4,5	XXXXXX	8.12.49	1	
Injektordüse Injector nozzle	mm	1,7	XXXXXX	4,5	XXXXXX	
Mahlluft (Stickstoff) Milling air (nitrogen)	bar	4	XXXXXX	1,7	XXXXXX	
Mahldüse Milling nozzle	mm	1,4	XXXXXX	4	XXXXXX	9.12.49
Einlaßdüse Inlet nozzle	mm	5	XXXXXX	1,4	XXXXXX	
Material Einlaßdüse Material inlet nozzle	XXXXXX	Teflon	XXXXXX	5	XXXXXX	
Auslaß outlet	mm	20	XXXXXX	Teflon	XXXXXX	
Material Auslaß Material outlet	XXXXXX	Teflon	XXXXXX	20	XXXXXX	
Schneckeneinstellung Screw adjusting	skt	dok.	XXXXXX	Teflon	XXXXXX	
Durchsatz Flow rate	g/min	60 - 100	XXXXXX	1,20	XXXXXX	
Ausführung (Datum/Unterschrift) Performance (Date/Signature)				3.12.49		


Inseriert am: 27.10.99

MYL_SOR00012622

BAYER AG PH-PD PCS	Herstellprotokoll Batch Manufacturing Record Seite 8	VM 01, Ausgabe 01
Material-Nr. Product No. 00 05407052	Materialbezeichnung Product name BAY 54-9085 MICRONIZED	Charge 527319 PART 1
Besondere Hinweise: Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske P3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen. Special notes: Use rubber gloves, safety glasses, ear protectors and dust mask P3. Water dangerous, must not get in the sewage. Protect from light.		

Anweisung

Probenziehung (jeweils 1g) : Sampling (each 1g) : 3 Proben (1 Anfang, 1 Mitte und 1 Ende) zur 3 Samples (1 beginning, 1 middle and 1 end) Korngrößenanalyse an PH-PD-QCD weiterleiten send to PH-PD-QCD for particle size distribution Methode: Laserbeugung (Sympatec, Rodos) Method: diffraction of laser (Sympatec, Rodos) - Analyseergebnisse den Herstellunterlagen beifügen - append analytical results to the manufacturing records
Datum: 8.12.99 Ausführer:  Date: Carried out by:

Parameter	Einheit Units	Richtwert Guideline	Istwert Actual value Anfang beginning		Istwert Actual value Mitte middle		Istwert Actual value Ende end	
X ₁₀	µm	dok.	0,66	0,65	0,68	0,66	0,68	0,67
X ₅₀	µm	dok.	1,45	1,44	1,37	1,39	1,41	1,40
X ₉₀	µm	dok.	3,83	3,88	4,70	5,67	3,77	3,74
Datum / Unterschrift: 13.12.99 								
Date/Signature								

BAYER AG PH-PD PCS	Herstellprotokoll Batch Manufacturing Record Seite 9	VM 01, Ausgabe 01
Material-Nr. Product No.	Materialbezeichnung Product name	Charge
00 05407052	BAY 54-9085 MICRONIZED	527319 PART 4
Besondere Hinweise: Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske P3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen. Special notes: Use rubber gloves, safety glasses, ear protectors and dust mask P3. Water dangerous, must not get in the sewage. Protect from light.		

Standard-Packmittel mikronisierter Wirkstoff Standard packaging material for micronized active substance				
Packmittelbezeichnung Packaging material	Volumen	PMR Product No.	Pt.Nr. Batch No.	Anzahl number
PA/PE-VERBUNDFOLIEN-FLACHSACK pa/pe flat sack	20 - 40 l	03 00072554	5342445	2
PA/PE-VERBUNDFOLIEN-FLACHSACK pa/pe flat sack	80 l	03 00910045	—	—
SCHWARZBLECH-HOBBOCK Black metal hobbock	30 l	03 00502338	XXXXXXXXXX	—
SCHWARZBLECH-HOBBOCK Black metal hobbock	60 l	03 00259441	XXXXXXXXXX	1
LDPE-FLACHSACK SCHWARZ 60L pe flat sack, black 60 litres	60 l	03 00261799	XXXXXXXXXX	—
LDPE-FLACHSACK SCHWARZ 120L pe flat sack, black 120 litres	120 l	03 00834535	XXXXXXXXXX	—
TROCKENMITTELBEUTEL 4 TME Desiccant	XXXXXXXXXX	03 00246692	XXXXXXXXXX	1
Datum / Unterschrift Date/Signature 8.12.99				

Lagerhinweise :

Notes for storage:

Vor Feuchtigkeit schützen. Protect from moisture. Vor Licht schützen. Protect from light. PA/PE-Beutel mit Trockenbeutel auf PA/PE-Innenbeutel in Schwarzblech-Hobbock. PA/PE bag in black metal drum with a desiccant on the inner PA/PE bag
Datum / Unterschrift Date/Signature 8.12.99

Anweisung


Instruction


- Musteretikett Endprodukt auf Folgeseite kleben - Affix sample label of final product on next page - nicht benötigte Etiketten vernichten - Destroy labels which are not required			
Etikettenbilanz Endprodukt			
Label balance, final product		verbrauchte Etiketten	3
ausgegebene Etiketten	12	Musteretikett	1
Labels issued		Speziallabel	8
nachbestellte Etiketten	0	vernichtete Etiketten	8
Labels ordered subsequently		Labels destroyed	
Summe	12	Summe	12
Total		Total	
Datum: 8.12.99 Ausführender:			

Druckdatum: 27.11.99

MYL_SOR00012624

BAYER AG PH-PD PCS	Herstellprotokoll Batch Manufacturing Record Seite 10	VM 01, Ausgabe 01
Material-Nr. Product No.	Materialbezeichnung Product name	Charge
00 05407052	BAY 54-9085 MICRONIZED	527319 PART 1
Besondere Hinweise: Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske P3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen. Special notes: Use rubber gloves, safety glasses, ear protectors and dust mask P3. Water dangerous, must not get in the sewage. Protect from light.		

Musteretikett Sample label:	
PH - PD - PCS Klinikmusterherstellung VM 01, Ausgabe 01	
Materialbez. : BAY 54-9085 MICRONIZED Material-Nr. : 00 05407052 Chargen-Nr. : .PART.	 Giftig
Gebinde:	von:
Tara:	Netto:
Vor Feuchtigkeit schützen. Vor Licht geschützt lagern.	
Etikett 23 von 24	

- zusätzlich oder nachträglich zum HP-Schein ausgedruckte Unterlagen (z.B. Etiketten, Anlagen) nach Art und Menge dokumentieren - record type and quantity of additional documents or those printed after the manufacturing protocol (e.g. labels, appendices) - Kopfdaten durch 2. Person überprüfen lassen - let the important data checked by a 2nd person			
Stk Pieces	Unterlage Document	ausgedruckt, am Printed, on	geprüft, am Checked, on
		7.12.99	
			

BAYER AG PH-PD PCS	Herstellprotokoll Batch Manufacturing Record Seite 11	VM 01, Ausgabe 01
Material-Nr. Product No. 00 05407052	Materialbezeichnung Product name BAY 54-9085 MICRONIZED	Charge 527315 PART 4
Besondere Hinweise: Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske P3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen. Special notes: Use rubber gloves, safety glasses, ear protectors and dust mask P3. Water dangerous, must not get in the sewage. Protect from light.		

Ausbeuteberechnung Mahlung Yield determination of milling				
	Einheit unit	Richtwert Guideline	Sollwert Required value	Istwert Actual value
Einwaage Wirkstoff Weighing of active substance	kg	2,37 / 16.07.12.99 -60,0-	XXXXXXXXXXXX	2,3749
- IPC Korngröße - IPC particle size	kg	dok.	XXXXXXXXXXXX	0,003
- Mahlrückstand - milling residue	kg	dok.	XXXXXXXXXXXX	0,01
Summe (= theor. Ausbeute) Sum (=theoretical yield)	kg	2,37 / 16.07.12.99 -60,0-	XXXXXXXXXXXX	2,3619
praktische Ausbeute Practical yield	kg	Waage-Nr.: Balance No.: 3		2,3622
praktische Ausbeute Practical yield	%	XXXXXXXXXXXX	90 - 100	100,0
Ausführung (Datum/Unterschrift) Carried out by (Date/Signature)		5.12.99 <i>mm</i>		
Übertrag und Berechnung überprüft: Transcription and calculation checked by:		08.12.99 <i>llk</i>		

Entnahmen Withdrawals	Einheit Units	Menge Amount	Restmenge Residue
Ausführung (Datum/Unterschrift) Carried out by (Date/Signature)			

BAYER AG / PH-PD PCS		Herstell. Protokoll Batch Manufacturing Record		Seite 12		VM 01, Ausgabe 01	
Material-Nr. Produkt-Nr. 00 05407052		Materialbezeichnung Produkt name BAY 54-9085 MICRONIZED				Charge K 27 279 H .PART.	
Besondere Hinweise: Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske P3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen. Special notes: Use rubber gloves, safety glasses, ear protectors and dust mask P3. Water dangerous, must not get in the sewage. Protect from light.							
Auswaage Ausbeute Probenziehung benachrichtigt (Datum/Zeichen): 13.12.99 100							
Mittelwert Tablettengewicht (mg): —							
Geb. (tablets)	Ans. sub lot	Waagen Nr. Balance no.:	Tara (kg) Tare (kg)	Brutto (kg) Gross (kg)	Netto vor Probenziehung (kg) Net before sampling (kg) = prakt. Ausbeute - Entnahmen - practical yield - Withdrawals	Zeichen Initials	Datum Date
1	1	3	5,063	7,4252	2,3622	10	9.12.99
2							
3							
4							
5							
6							
7							
8							
						Menge nach Probenziehung Amount after sampling kg, tSt, Stk (kg, 1000 pcs., pcs.) 2,348	
						Gesamtmenge Total amount kg, tSt, Stk (kg, 1000 pcs., pcs.) 99,072	
14.12.99 100 Fertigungsauftrag abgerechnet (AV) Production order completed (Planning Department) (AV)							
Ausbeute bezogen auf Auftragsgröße Yield with reference order size:							
14.12.99 100 Probenziehung durchgeführt (QC) Sampling performed (QC)							

BAYER AG / PH-PD PCS		Herstellprotokoll		Seite 1		VM 01, Ausgabe 01	
Material-Nr. 00 05407052		Materialbezeichnung BAY 54-9085 MICRONIZED				Charge 527319 4 .PART.	
Besondere Hinweise: Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske P3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen. Special notes: Use rubber gloves, safety glasses, ear protection and dust mask P3. Water dangerous, must not get in the sewage. Protect from light.							

Befund Herstellung

Prüfpunkte	Herstellung		Gerätestatus		Betriebsmittelprüfung		Inprozesskontrollen		Ausbeute Stufe [kg,Stk]			Herstellung entsprechend Herstellanweisung	
	Beginn	Ende	Status	Gerät	entspricht	entspricht nicht	entspricht	entspricht nicht	Eingangsmenge	praktische Ausbeute	Anteil zum Einsatz	entspricht	entspricht nicht
Einwaage Granulation / Mischung	8.12.99	9.12.99	XXXXXXXXXXXX		X		XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX	2,37	1	X	
Granulation / Mahlung (incl. Feststoffan- Grav./flüssigkeit)			0 1 0 2 0 3							= %	XXXXXXXXXX	16.12.99	
Einwaage Nachmischung (incl. Vormischung)			XXXXXXXXXXXX				XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX				T
Tablettierung / Verkapselung			0 1 0 2 0 3							= %	XXXXXXXXXX		
Einwaage Lackierung			XXXXXXXXXXXX				XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXX				
Lackierung (incl. Sprühdüse)			0 1 0 2 0 3							= %	XXXXXXXXXX		
16.12.99 Abfüllung Flaschen	8.12.99	12.12.99	X 1 0 2 0 3		X		X		2,37	2,36 99,6	1	X	

1 = fliegender Chargenwechsel, 2 = Produktwechsel mit Zwischenreinigung, 3 = Reinigung gemäß ANW

1 = fliegender Chargenwechsel, 2 = Produktwechsel mit Zwischenreinigung, 3 = Reinigung gemäß AW

BAYER AG / PH-PD PCS		Herst. protokoll Batch Manufacturing Record		Seite 14	VM 01, Ausgabe 01
Material-Nr. Product No.		Materialbezeichnung Product name		Charge	
00 05407052		BAY 54-9085 MICRONIZED		15.03.19 H .PART.	
Besondere Hinweise: Gummihandschuhe, Schutzbrille, Gehörschutz und Vollmaske p3 tragen. Wassergefährdend, darf nicht in die Kanalisation gelangen. Vor Licht schützen. Special notes: Use rubber gloves, safety glasses, ear protectors and dust mask p3. Water dangerous, must not get in the sewage. Protect from light.					

Manufacturing report

Control point	Manufacturing		Equipment status		Working material check		Inprocess control		Yield level [kg, pieces]			Manufacturing complies the manufacture instruction	
	Beginning	End	Status	Equipment	Complies	Does not comply	Complies	Does not comply	Starting amount	Practical yield	Portion for use	Complies	Does not comply
Level													
Weighting Granulation / Mixing			XXXXXXXXXXXXXXXXXX				XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXXXXXX				
Granulation / Milling (incl. solid fraction of gran. fluid)			0 1 _____ 0 2 _____ 0 3 _____								XXXXXXXXXX		
										= %			
Weighting post blend (incl. problem)			XXXXXXXXXXXXXXXXXX				XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXXXXXX				
Tabletting / Encapsulation			0 1 _____ 0 2 _____ 0 3 _____								XXXXXXXXXX		
										= %			
Weighting Coating			XXXXXXXXXXXXXXXXXX				XXXXXXXXXX	XXXXXXXXXX	XXXXXXXXXXXXXX				
Coating (incl. spray loss)			0 1 _____ 0 2 _____ 0 3 _____								XXXXXXXXXX		
										= %			
Filling			0 1 _____ 0 2 _____ 0 3 _____										
										= %			

1 = flying batch change, 2 = product change with intermediate cleaning, 3 = cleaning according to Regulation

1 = flying batch change, 2 = product change with intermediate cleaning, 3 = cleaning according to Regulation

PH - PD - PCS Klinikmusterherstellung
VH 01, Ausgabe 01

Einsatzstoff für

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART.

527319 H

Einsatzstoff : BAY 54-9085
 Material-Nr. : 00 05381339
 Chargen-Nr. :

Anlage 3 bestehend
 aus 6 Blättern

Ansatz:

von:

Netto:

16.12.99

Etikett 1 von 24

PH - PD - PCS Klinikmusterherstellung

VH 01, Ausgabe 01

Einsatzstoff für

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART.

527319 H

Einsatzstoff : BAY 54-9085
 Material-Nr. : 00 05381339
 Chargen-Nr. :

Ansatz:

von:

Netto:

Etikett 2 von 24

PH - PD - PCS Klinikmusterherstellung

VH 01, Ausgabe 01

Geräteetikett für

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART.

527319 H

Ansatz:

von:

Datum:

Etikett 3 von 24

PH - PD - PCS Klinikmusterherstellung

VH 01, Ausgabe 01

Geräteetikett für

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART.

527319 H

Ansatz:

von:

Datum:

Etikett 4 von 24

MYL_SOR00012631

PH - PD - PCS Klinikmusterherstellung

VN 01, Ausgabe 01

Einwaage für

Materialbez. : BAY 54-9085 MICRONIZED
Material-Nr. : 00 05407052
Chargen-Nr. : .PART.

527316 H

Einwaagebeginn

Datum:

Zeichen:

Kabine gereinigt

Datum:

Zeichen:

Etikett 5 von 24

PH - PD - PCS Klinikmusterherstellung

VN 01, Ausgabe 01

Einwaage für

Materialbez. : BAY 54-9085 MICRONIZED
Material-Nr. : 00 05407052
Chargen-Nr. : .PART.

527316 H

Einwaagebeginn

Datum:

Zeichen:

Kabine gereinigt

Datum:

Zeichen:

Etikett 6 von 24

PH - PD - PCS Klinikmusterherstellung

VN 01, Ausgabe 01

Einwaage für

Materialbez. : BAY 54-9085 MICRONIZED
Material-Nr. : 00 05407052
Chargen-Nr. : .PART.

527316 H

Einwaagebeginn

Datum:

Zeichen:

Kabine gereinigt

Datum:

Zeichen:

Etikett 7 von 24

PH - PD - PCS Klinikmusterherstellung

VN 01, Ausgabe 01

Einwaage für

Materialbez. : BAY 54-9085 MICRONIZED
Material-Nr. : 00 05407052
Chargen-Nr. : .PART.

527316 H

Einwaagebeginn

Datum:

Zeichen:

Kabine gereinigt

Datum:

Zeichen:

MYL_SOR00012632

PH - PD - PCS Klinikmusterherstellung
VN 01, Ausgabe 01

Geräteetikett für

Materialbez. : BAY 54-9085 MICRONIZED
Material-Nr. : 00 05407052
Chargen-Nr. : .PART.

527319 H

Ansatz:

von:

Datum:

Etikett 9 von 24

PH - PD - PCS Klinikmusterherstellung
VN 01, Ausgabe 01

Geräteetikett für

Materialbez. : BAY 54-9085 MICRONIZED
Material-Nr. : 00 05407052
Chargen-Nr. : .PART.

527319 H

Ansatz:

von:

Datum:

Etikett 10 von 24

PH - PD - PCS Klinikmusterherstellung
VN 01, Ausgabe 01

Geräteetikett für

Materialbez. : BAY 54-9085 MICRONIZED
Material-Nr. : 00 05407052
Chargen-Nr. : .PART.

527319 H

Ansatz:

von:

Datum:

Etikett 11 von 24

PH - PD - PCS Klinikmusterherstellung
VN 01, Ausgabe 01

Geräteetikett für

Materialbez. : BAY 54-9085 MICRONIZED
Material-Nr. : 00 05407052
Chargen-Nr. : .PART.

527319 H

Ansatz:

von:

Datum:

Etikett 12 von 24

MYL_SOR00012633

PH - PD - PCS Klinikmusterherstellung

VN 01, Ausgabe 01

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART. 527319 H

Gebinde: von:

Tara: Netto:

Vor Feuchtigkeit schützen.
 Vor Licht geschützt lagern.

Etikett 13 von 24

PH - PD - PCS Klinikmusterherstellung

VN 01, Ausgabe 01

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART. 527319 H

Gebinde: von:

Tara: Netto:

Vor Feuchtigkeit schützen.
 Vor Licht geschützt lagern.

Etikett 14 von 24

PH - PD - PCS Klinikmusterherstellung

VN 01, Ausgabe 01

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART. 527319 H

Gebinde: von:

Tara: Netto:

Vor Feuchtigkeit schützen.
 Vor Licht geschützt lagern.

Etikett 15 von 24

PH - PD - PCS Klinikmusterherstellung

VN 01, Ausgabe 01

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART. 527319 H

Gebinde: von:

Tara: Netto:

Vor Feuchtigkeit schützen.
 Vor Licht geschützt lagern.

Etikett 16 von 24

MYL_SOR00012634

PH - PD - PCS Klinikmusterherstellung
VN 01, Ausgabe 01

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART.

527319 H

Gebinde: von:

Tara: Netto:

Vor Feuchtigkeit schützen.
 Vor Licht geschützt lagern.

Etikett 17 von 21

PH - PD - PCS Klinikmusterherstellung
VN 01, Ausgabe 01

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART.

527319 H

Gebinde: von:

Tara: Netto:

Vor Feuchtigkeit schützen.
 Vor Licht geschützt lagern.

Etikett 18 von 24

PH - PD - PCS Klinikmusterherstellung
VN 01, Ausgabe 01

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART.

527319 H

Gebinde: von:

Tara: Netto:

Vor Feuchtigkeit schützen.
 Vor Licht geschützt lagern.

Etikett 19 von 24

PH - PD - PCS Klinikmusterherstellung
VN 01, Ausgabe 01

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART.

527319 H

Gebinde: von:

Tara: Netto:

Vor Feuchtigkeit schützen.
 Vor Licht geschützt lagern.

Etikett 20 von 24

PH - PD - PCS Klinikmusterherstellung
VH 01, Ausgabe 01

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART. 527319 H

Gebinde: von:

Tara: Netto:

Vor Feuchtigkeit schützen.
 Vor Licht geschützt lagern.

Etikett 21 von 24

PH - PD - PCS Klinikmusterherstellung
VH 01, Ausgabe 01

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART. 527319 H

Gebinde: von:

Tara: Netto:

Vor Feuchtigkeit schützen.
 Vor Licht geschützt lagern.

Etikett 22 von 24

PH - PD - PCS Klinikmusterherstellung
VH 01, Ausgabe 01

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART. 527319 H

Gebinde: von:

Tara: Netto:

Vor Feuchtigkeit schützen.
 Vor Licht geschützt lagern.

Etikett 23 von 24

PH - PD - PCS Klinikmusterherstellung
VH 01, Ausgabe 01

Materialbez. : BAY 54-9085 MICRONIZED
 Material-Nr. : 00 05407052
 Chargen-Nr. : .PART. 527319 H

Gebinde: von:

Tara: Netto:

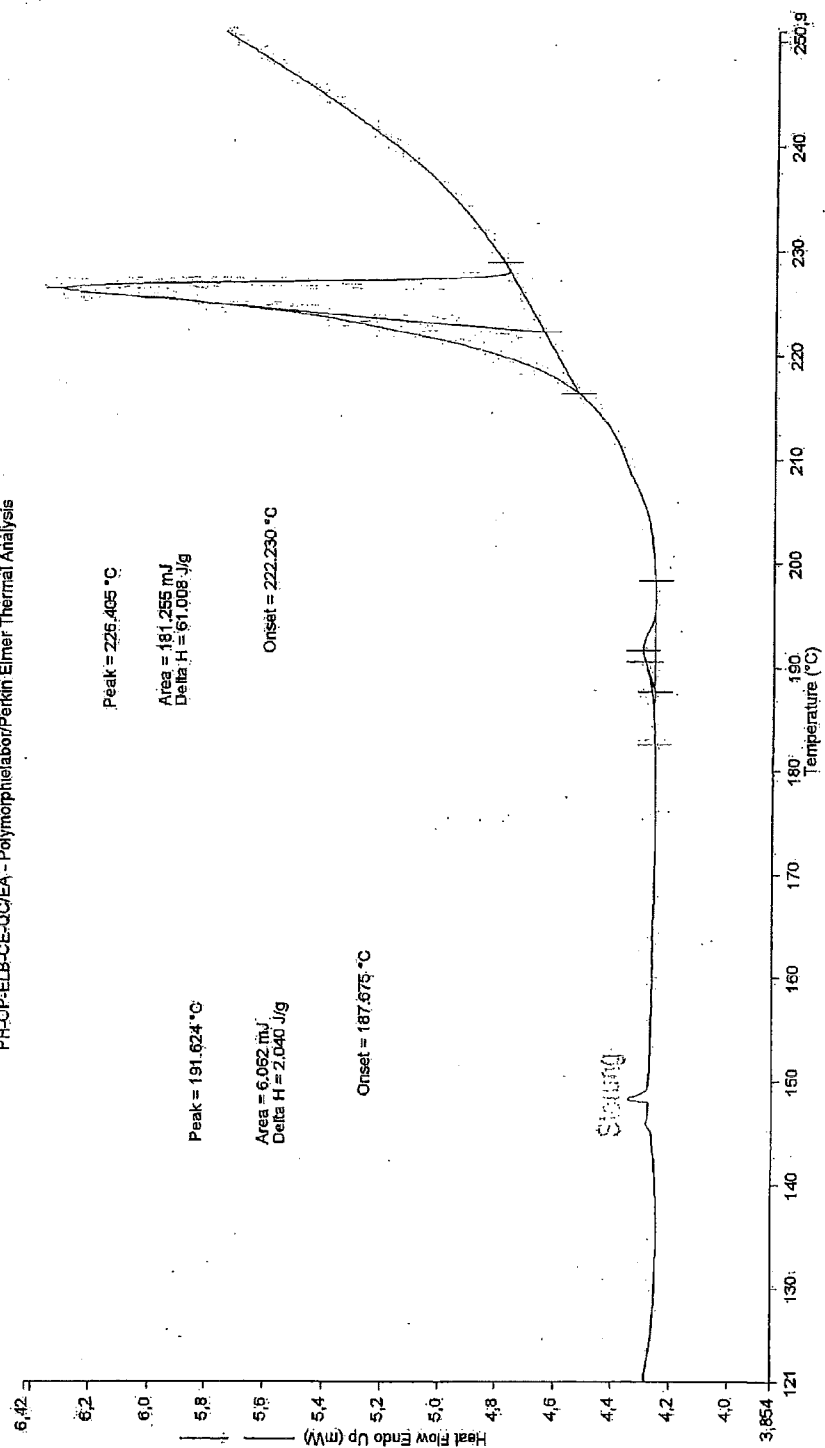
Vor Feuchtigkeit schützen.
 Vor Licht geschützt lagern.

Etikett 24 von 24

Filename: C:\PE\Pyris\Data\pyr2476.dod
 Data Collected: 21.12.99 16:17:26
 Baseline Filename: C:\PE\Pyris\Data\base121.dod
 Operator ID: Kell
 Sample ID: Bay 54-9085 mkr. - Pt. 527319H Dr. Brehm
 Sample Weight: 2.971 mg
 Comment: DSC-Pyris1(155239);AM-AAL572-035-180181
 N2-Ström;Al-Tiegel perforiert;SET:21.12.99

22.12.99
 Berechnung und Überprüfung
 geprüft: 22.12.99

PH-OP-ELB-CE-QC/EA - Polymorphielabor/Perkin Elmer Thermal Analysis



1) Heat from 120.00 °C to 250.00 °C at 2.00 °C/min

22.12.99 08:13:39

Enclosure 8

EXHIBIT 5

REDACTED
IN ITS
ENTIRETY

EXHIBIT 6

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

BAYER HEALTHCARE LLC, BAYER
HEALTHCARE PHARMACEUTICALS INC.,
and ONYX PHARMACEUTICALS, INC.,

Plaintiffs,

v.

MYLAN PHARMACEUTICALS INC. and
MYLAN INC.,

Defendants.

Civil Action No. 1:15-cv-114

EXPERT REPORT OF MICHAEL GROSSBARD, M.D.

I. BACKGROUND

Professional Background and Qualifications

1. My name is Dr. Michael L. Grossbard. I received a Bachelor of Arts in Biology, *summa cum laude*, in 1982 from Harvard College in Cambridge, Massachusetts and a Doctor of Medicine, *cum laude*, in 1986 from Yale University School of Medicine in New Haven, Connecticut. From 1986 to 1987, I performed my internship in internal medicine at the Massachusetts General Hospital in Boston, Massachusetts. From 1987 to 1989, I served my residency in Internal Medicine at Massachusetts General Hospital. From 1989 to 1991, I was a fellow in medical oncology at the Dana-Farber Cancer Institute and a clinical fellow in medicine at Harvard Medical School in Boston, Massachusetts. I am board certified in Internal Medicine and Medical Oncology by the American Board of Internal Medicine.

2. My professional career has included the following positions and faculty appointments:

- Clinical Associate, Dana-Farber Cancer Institute, Boston, MA
- Attending Physician, Bone Marrow Transplant Service, Dana-Farber Cancer Institute, Boston, MA
- Attending Physician, Medical Oncology, Massachusetts General Hospital, Boston, MA
- Assistant in Medicine, Massachusetts General Hospital, Boston, MA
- Attending Physician, Medical Service, Massachusetts General Hospital, Boston, MA
- Assistant Physician, Massachusetts General Hospital, Boston, MA
- Associate Director, Continuum Cancer Centers of New York
- Associate Attending Physician, St. Luke's-Roosevelt Hospital Center, New York, NY
- Senior Attending Physician, St. Luke's-Roosevelt Hospital Center
- Attending Physician, Beth Israel Medical Center, New York, NY
- Attending Physician, Mount Sinai Hospital, New York, NY
- Instructor in Medicine, Harvard Medical School, Boston, MA
- Assistant Professor of Medicine, Harvard Medical School, Boston, MA
- Associate Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons
- Professor of Clinical Medicine, Columbia University College of Physicians and Surgeons
- Professor of Medicine at Columbia University Medical Center
- Visiting Associate Professor of Medicine, Albert Einstein College of Medicine

- Visiting Professor of Medicine, Albert Einstein College of Medicine
- Professor of Medicine, Icahn School of Medicine at Mount Sinai
- Professor of Medicine, NYU School of Medicine

3. Between 2000 and 2014, I served as the Chief of Hematology and Oncology at St. Luke's-Roosevelt Hospital and Beth Israel Medical Center in New York. I provided primary oncologic care to more than 250 newly diagnosed cancer patients each year. In addition, I supervised the training of Hematology and Oncology fellows on a daily basis and, in that capacity, was involved in the care of another 250-500 cancer cases each year. My academic and clinical interests during that time period were broad, but involved the care of patients with both solid tumors and hematologic malignancies.

4. Since September 2014, I have been the Director of the Hematologic Malignancies Clinical Program at the Perlmutter Cancer Center at NYU. However, I also served as the Interim Chief of Hematology/Oncology from 1/2015 until 12/2016. Since January 2015 (and continuing through the present) I have served as the Section Chief for Hematology/Oncology at Tisch Hospital of NYU Langone Medical Center and am responsible for directing the in-patient service that provides care for patients with both solid tumors and hematologic malignancies.

5. I am a member of the American Society of Clinical Oncology and American Society of Hematology. I have served on data safety and monitoring boards and independent trial review committees for several cancer medications, including VX710, a novel agent for the therapy of hepatocellular carcinoma. I also have participated on numerous hospital committees. I have lectured at many seminars and have served as an editor for several journals relating to the field of medical oncology and hematology. I have published more than 60 original scholarly works in peer-

reviewed journals, including multiple publications relating to solid tumors and two relating specifically to genitourinary malignancies. I have published more than 50 review articles and have edited two books and authored several book chapters. I also have significant experience with drug development and clinical trials.

6. My areas of expertise, based on my training, experience, and research, include the following areas of medical oncology: hematologic malignancies (including program leadership) and solid tumors (program leadership in thoracic oncology, gastrointestinal oncology, and breast oncology programs at various times in my career).

7. In preparing this report, I have relied on my knowledge, training, and experience, the documents cited herein, and the opinions expressed in the Opening Report of Dr. Mark Hollingsworth, Ph.D. (“Hollingsworth Op. Rep.”) and the Opening Report of Dr. Ron Bihovsky, Ph.D. (“Bihovsky Op. Rep.”).

8. A current copy of my curriculum vitae is attached as **Exhibit A**.

Compensation and Prior Testimony

9. I have been retained by counsel for Mylan Pharmaceuticals Inc. (“Mylan”) as an expert consultant and potential trial witness. For my work on this matter, I am being compensated at my standard consulting rate of \$750 per hour (\$6000 per day for trial testimony and depositions).

10. In the last four years, I have testified as an expert at trial or by deposition as detailed **in Exhibit B**.

II. ASSERTED CLAIMS AND SUMMARY OF OPINIONS

11. If called as an expert witness in this matter, I anticipate that my testimony may concern the matters addressed below. Additionally, since this report addresses only validity issues, I

anticipate that I may comment on materials relating to these topics that later become available, such as expert reports or deposition testimony. I reserve the right to supplement or amend this report, including by rebutting or agreeing with opinions expressed in reports by other experts. In connection with my testimony, I may present visual aids and demonstrative exhibits that illustrate the analysis discussed in this report.

12. I understand that Bayer Healthcare LLC, Bayer Healthcare Pharmaceuticals Inc., and Onyx Pharmaceuticals, Inc. (“plaintiffs”) are asserting six patents against Mylan in this litigation: U.S. Patent No. 8,618,141 (“the ’141 patent”), U.S. Patent No. 7,897,623 (“the ’623 patent”), U.S. Patent No. 7,235,576 (“the ’576 patent”), U.S. Patent No. 7,351,834 (“the ’834 patent”), U.S. Patent No. 8,877,933 (“the ’933 patent”), and U.S. Patent No. 8,841,330 (“the ’330 patent”). For purposes of my report, I have focused on the ’141 patent, the ’330 patent, and the ’933 patent.

13. I understand that the plaintiffs are asserting the following claims against Mylan: claims 7-9 of the ’141 patent, claims 4, 10, 13, and 14 of the ’330 patent, and claims 1-2, 8-10, 16, 18-19, 21, and 28-29 of the ’933 patent.

14. I have been asked to give my opinion regarding the validity of claims 7-9 of the ’141 patent, claims 4, 10, 13, and 14 of the ’330 patent, and claims 8-10, 16, 18-19 and 21 of the ’933 patent.

The ’141 and ’330 Patents

15. It is my opinion that claims 7-9 of the ’141 patent are invalid as anticipated by the prior art.

16. It is my opinion that claims 8 and 9 of the ’141 patent are invalid under 35 U.S.C. § 112 because they lack sufficient written description and/or lack of enablement because the ’141

patent does not contain any description of tumors that possess “abnormal angiogenesis or hyperpermiability processes that are not p38-mediated or raf-mediated.”

17. It is my opinion that claims 8 and 9 of the ’141 patent are invalid under 35 U.S.C. § 112 because the phrase “hyperpermiability processes” is indefinite.

18. It is my opinion that claims 8 and 9 of the ’141 patent are indefinite for lacking antecedent basis.

19. It is my opinion that claims 8 and 9 of the ’141 patent are invalid under 35 U.S.C. § 101 for failing to disclose any new or useful methods of treatment or improvement thereof.

20. It is my opinion that claims 4, 10, 13, and 14 of the ’330 patent are invalid under 35 U.S.C. § 112 for inadequate written description and/or lack of enablement, because the specification does not sufficiently describe how sorafenib can be used to treat tumors or cancer of the prostate, breast, liver, ovary, or cervix, and does not demonstrate to one of ordinary skill in the art that the named inventors had possession of methods of treating cancer.

21. It is my opinion that claims 7-9 of the ’141 patent and claims 4, 10, 13, and 14 of the ’330 patent disclose methods of treatment that would have been obvious to a person of skill in the art.

22. It is my opinion that the specifications of the ’141 and the ’330 patents would not have taught a person of skill in the art at the time of filing how to practice the full scope of the invention disclosed in claims 7-9 of the ’141 patent and claims 4, 10, 13, and 14 of the ’330 patent without undue experimentation.

23. It is my opinion that the specifications of the ’330 and ’141 patents fail to disclose a manner and process of “administering . . . an effective amount” in “full, clear, concise, and exact

terms” as to enable a POSA to practice the invention, nor do the claims of the ’330 and ’141 patents “particularly point[] out and distinctly claim[] the subject matter which the applicant regards as his invention.”

24. It is my opinion that the disclosed range of 0.01 mg/kg–200 mg/kg does not allow a POSA to practice the invention without undue experimentation, therefore rendering claims 4, 10, 13, and 14 of the ’330 patent and claims 7-9, and 11 of the ’141 patent invalid under § 112 for lack of enablement, inadequate written description, and indefiniteness.

The ’933 Patent

25. It is my opinion that claims 8-10 of the ’933 patent are invalid for being anticipated by WO 03/068228.

26. It is my opinion that claims 8-10 of the ’933 patent are rendered obvious by WO 03/068228 in view of U.S. Patent App. Pub. No. 2003/0232765 to Carter et al.

27. It is my opinion that claims 10, 16, 18-19, 21, 41 are invalid for double patenting over U.S. Patent No. 7,351,834.

28. It is my opinion that claims 10, 16, 18-19 and 21 are obvious variants of claims 7-9 of U.S. Patent No. 8,618,141.

III. TUTORIAL

29. For the purposes of preparing for my consultation and potential witness services, I have reviewed relevant literature and materials, which are listed in **Exhibit C**.

30. I provide a tutorial below, which reflects what was known by a person of ordinary skill in the art (“POSA”).

Tumor Biology

31. A tumor is an abnormal mass of tissue. Tumors can be benign or malignant. In a malignant tumor, the growth becomes excessive and is uncoordinated with the growth of normal tissues. Malignant tumors can continue to proliferate even after cessation of the stimuli which evoked the tumor. A tumor is considered purposeless, and its growth can be virtually autonomous. Connolly, et al., “Principles of Cancer Pathology,” Cancer Medicine 4th ed., Vol. 1 (Holland, et al., eds. Williams & Wilkins), Ch. 31 (1997), at 533-534.

32. Physicians divide cancer into two main types: solid tumors and liquid tumors (also known as blood-born cancers). Solid tumors refer to tumors that lack a cystic or liquid area. These tumors arise from organs and connective tissue, and different types of solid tumors are named for the cells that form them. For example, sarcomas arise from connective tissue, and adenocarcinomas arise from glandular structures in epithelial tissues. In contrast, liquid tumors refer to abnormal proliferation of the hematopoietic and lymphoid tissues, and include cancers like leukemia (hematopoietic precursor cells), lymphoma (lymphocytes) and myeloma (plasma cells).

33. Solid tumors may be benign (not cancer), or malignant (cancer). Le Beau, M.L., “Molecular Biology of Cancer: Cytogenetics,” Cancer Principles & Practices of Oncology 5th ed. (DeVita, et al., eds. Lippincott-Raven), Ch. 5 (1997), at 112-115.

34. Carcinomas are tumors that form in epithelial cells. Epithelial cells are found in the skin, glands and the linings of organs. Fenton, R.G. & D.L. Longo, “Cell Biology of Cancer,” Harrison’s Principles of Internal Medicine 14th ed., Vol. 1 (Fauci, et al., eds. McGraw-Hill), Ch. 83 (1998) (“Fenton”), at 505. Those organs include the bladder, ureters, lung, stomach, colon, breast, liver, ovary, cervix, prostate, and kidney.

35. Sarcomas are tumors that do not form in epithelial cells (i.e., originate in bone, fat tissue, ligament, muscle or tendon. There also are sarcomas that arise from the endothelial cells of blood vessels; *e.g.*, angiosarcoma). *Id.*

a. How Tumors Spread and Survive

36. Angiogenesis is the formation of new blood vessels. This process involves the migration, growth, and differentiation of endothelial cells, which line the inside wall of blood vessels. Folkman, J., “Tumor Angiogenesis,” *Cancer Medicine* 4th ed., Vol. 1 (Holland, et al., eds. Williams & Wilkins), Ch. 10 (1997) (“Folkman”). When angiogenesis is considered with respect to tumor blood vessel formation, it is referred to as tumor angiogenesis.

37. The process of angiogenesis is controlled by chemical signals in the body. These signals can stimulate both the repair of damaged blood vessels and the formation of new blood vessels. Other chemical signals, called angiogenesis inhibitors, interfere with blood vessel formation. Normally, the stimulating and inhibiting effects of these chemical signals are balanced so that blood vessels form only when and where they are needed. *Id.*

38. Angiogenesis plays a critical role in the growth and spread of cancer. A typical epithelial tumor cell measures approximately 8 um. When tumor cells are more than 150-200 uM from a nutrient vessel, their nutrition may be inadequate. Fidler, I.J., “Molecular Biology of Cancer: Invasion and Metastasis,” *Cancer Principles & Practices of Oncology* 5th ed. (DeVita, et al., eds. Lippincott Raven), Ch. 7 (1997), at 136. Indeed, an adequate blood supply is necessary for tumors to obtain nutrition, especially as they increase in size beyond a few millimeters. *Id.* at 135-136. Tumors can cause this blood supply to form by giving off chemical signals that stimulate angiogenesis. Tumors also can stimulate nearby normal cells to produce angiogenesis signaling molecules. The

resulting new blood vessels “feed” growing tumors with oxygen and nutrients, allowing the cancer cells to invade nearby tissue, to move throughout the body, and to form new colonies of cancer cells, called metastases. *Id.* at 136-144; *see also* Buolamwini, John, “Novel anticancer drug discovery.” *Current Opinion in Chemical Biology* 3:500-509, 505-506, 1999.

39. Because solid tumors cannot grow beyond a certain size or spread without a blood supply, a POSA would have looked for ways to block tumor angiogenesis, as early as the late 1990s. A POSA would have known to study angiogenesis inhibitors, also called antiangiogenic agents, with the idea that these molecules will prevent or slow the growth of cancer. *See generally*, Folkman, J., “Antiangiogenic Therapy,” *Cancer Principles & Practices of Oncology* 5th ed. (DeVita, et al., eds. Lippincott Raven), Ch. 64 (1997); Rak, et al., “Oncogenes as inducers of tumor angiogenesis,” *Cancer and Metastasis Reviews*, 14:263-277 at 263 (1995) (“Rak”)); Buolamwini at 505-506.

40. Kidney tumors typically are detected by ultrasound, CT scans, or MRIs. These tumors are identified when a physician requests the imaging to evaluate a clinical suspicion of renal cancer in the setting of flank pain or hematuria. Alternatively, renal cell carcinomas (“RCC”) can be identified as an incidental finding when an imaging test is ordered for another reason. Before 2000, the limit of resolution for these scans was 5-10 mm. Thus, tumors below this range were rarely detected. In fact, with respect to the kidney tumors that are relevant to this report, these solid tumors would have measured more than 10 mm in almost all circumstances and angiogenesis would, of necessity, have played a major role in their proliferation and propagation. Indeed, the inventors of the ’141 patent state that “[a]ngiogenesis is regarded as an absolute prerequisite for the growth of tumors beyond 1-2 mm.” ’141 patent at 2:1-2.

Mechanistic Pathways

41. The behavior of every cell in the body was known to a POSA to be tightly regulated by extracellular signals that determine whether the cell will live or die, differentiate, proliferate, or remain quiescent. These extracellular signals were known to regulate the cell by interacting with corresponding receptors on the cell surface that would then communicate to intracellular macromolecules the status of their occupancy. This was known to initiate flow of information through a series of signal transduction pathways that would ultimately result in modulation of cell function. Fenton, R.G. & D.L. Longo, “Cell Biology of Cancer,” Harrison’s Principles of Internal Medicine 14th ed., Vol. 1 (Fauci, et al., eds. McGraw-Hill), Ch. 83 at 507-510 (1998 (“Fenton”)); Hannun, Y.A., “Signal Transduction in Cancer,” Cancer Medicine 4th ed., Vol. 1 (Holland, et al., eds. Williams & Wilkins), Ch. 4 (1997) (“Hannun”), at 66.

42. One way in which receptors were known to transmit these extracellular signals was by acting as protein kinases. A protein kinase was known to be an enzyme that catalyzed the transfer of a phosphate group from a nucleoside triphosphate (e.g., adenosine triphosphate, or “ATP”), a molecule located in the intracellular environment, either to itself (autophosphorylate) or to another specified molecule, most often an amino acid on another protein. The process of phosphorylation was known to result in conformational changes in the target substrates with significant functional effects including activation or inhibition of other kinases, metabolic enzymes, and/or transcription factors. This, in turn, would cause a highly complex series of reactions known in the art as a signal transduction cascade. The signal transduction cascade could trigger such processes as cell survival, mitosis (i.e., cell replication and division), or apoptosis (i.e., cell death). *See, e.g.,* Heimbrook, et al.,

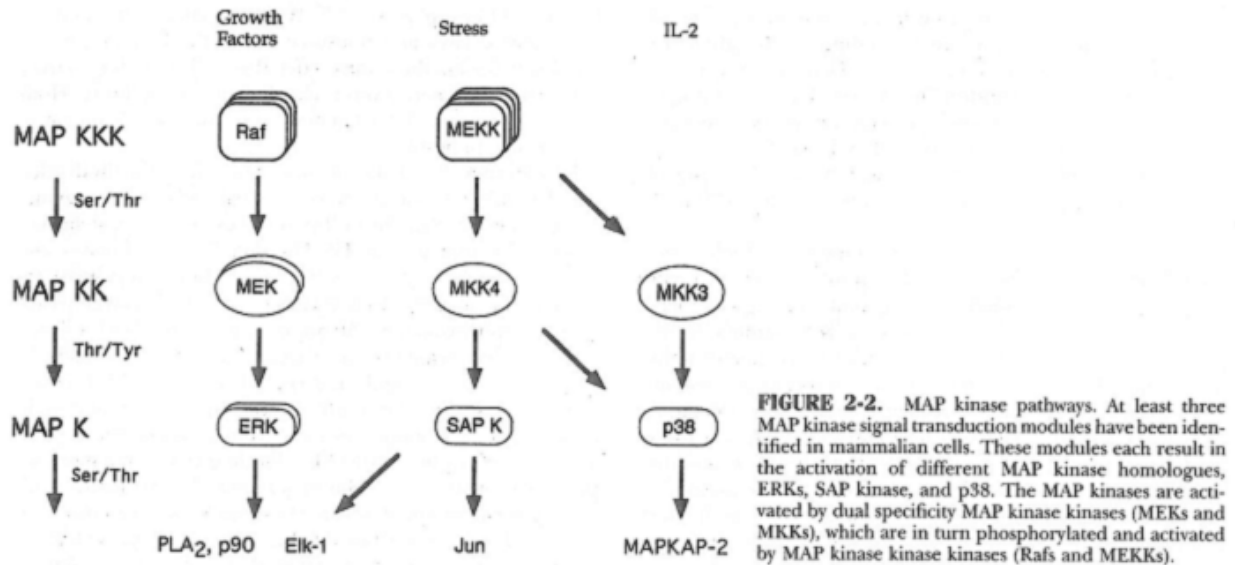
“Essentials of Signal Transduction,” *Cancer Principles & Practice of Oncology* 5th ed. (DeVita, et al., eds. Lippincott-Raven), Ch. 2 (1997) (“Heimbrook”), at 39-40; Hannun at 69-71.

43. Receptor-regulated cell signaling by way of protein kinases was known to be necessary for the normal function and replication of cells. However, it was also known that overstimulation of cells could disrupt the normal balance between mitosis and apoptosis, leading to uncontrolled cell replication. As uncontrolled cell replication leads to tumor growth, one skilled in the art might have found it desirable to inhibit the signaling pathway. Fenton at 507.

44. For example, a POSA might have looked to the structure of the ligand-binding site on the receptor and tried to block this site, which could prevent the extracellular signal from binding, and, in turn, stop the receptor from functioning as a kinase. However, genetic mutations found in many cancers were known to lead to receptors whose kinase function was turned “on” even in the absence of ligand. Thus, another strategy would have been to look at the intracellular structure of the protein kinase and block its ATP-binding site, which would in turn stop the receptor from binding to the ATP that would otherwise cause phosphorylation. Fedi, et al., “Growth Factors,” *Cancer Medicine* 4th ed., Vol. 1 (Holland, et al., eds. Williams & Wilkins), Ch. 3 (1997), at 56-57. It was known that the drug compounds at issue in this case acted in this latter manner.

45. One set of protein kinases, receptor tyrosine kinases (“RTKs”), were known to catalyze phosphorylation through tyrosine amino acid residues. RTKs have long been known to be potential targets in the treatment of cancer. Specifically, a POSA would have known that to block this phosphorylation, one could target the signaling molecules responsible for activating the signal transduction cascade. These signaling molecules included raf and p38 kinases. Fenton at 508-509;

Buolamwini at 501-502; Herlaar, E. & Z. Brown “p38 MAPK signaling cascades in inflammatory disease,” *Molecular Medicine Today*, 5:439-447, 440-443 (1999) (“Herlaar”).



Heimbrook at 40.

i. VEGFR/KDR-Mediated Pathway

46. One set of extracellular signals known to bind to RTKs were the vascular endothelial growth factors (“VEGF”). Fauci, et. al., *Principles of Internal Medicine* 508, 14th ed. 1998.

47. As discussed above, when tumors reach a certain size, they require additional blood supply to be viable. That blood supply requires the growth of new blood vessels that provide for the tumor. Therefore, by the late 1990s, it was demonstrated that angiogenesis in tumor formation was mediated by up-regulation of VEGF receptors (“VEGFR”). Folkman at 192; Rak at 263; Ellis, et. al., “Vascular Endothelial Growth Factor in Human Colon Cancer: Biology and Therapeutic Implications,” *The Oncologist*, 5(Suppl. I):11-15, 11 (2000).

48. When VEGF and other endothelial growth factors bind to their receptors on endothelial cells, signals within these cells are initiated that promote the growth and survival of new

blood vessels (i.e., angiogenesis). Holland, J. et. al., Cancer Medicine Chap. 10, 4th ed. 1997; Rak, J. et al., “Oncogenes as inducers of tumor angiogenesis.” Cancer and Metastasis Reviews 14:263-277, 265, 1995.

49. It became known that sorafenib tosylate could be used to treat “diseases in humans or other mammals which are mediated by the VEGF induced signal transduction pathway, including those characterized by abnormal angiogenesis or hyperpermiability processes.” WO 03/068228 (“WO 228”) at 4. These methods include administering a compound of formula I below or a salt, prodrug or stereoisomer thereof to a human or other mammal with a disease characterized by abnormal angiogenesis or hyperpermiability processes. *Id.* WO 228 also discloses that the compounds of the patent “may be administered orally, topically, parenterally, by inhalation or spray or vaginally, sublingually, or rectally in dosage unit formulations.” *Id.* at 25. WO 228 also discloses the use of numerous pharmaceutically acceptable excipients. *Id.* at 26.

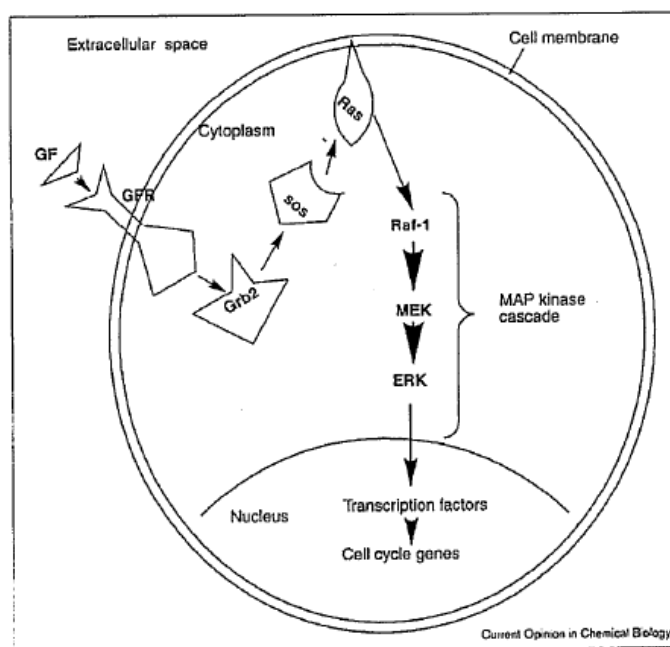
50. Claim 22 of WO 228 specifically discloses sorafenib tosylate and a method of using it: “A method of treating disease mediated by VEGF-induced signal transduction pathway comprising administering N-(4-chloro-3-(trifluoromethyl) phenyl)-N’-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea tosylate.” *Id.* at 75. The body of WO 228 discloses sorafenib tosylate free base and a method of making it as Example B. It also discloses 4-toluene sulfonic acid as a potential salt-forming acid, which is also known as para- or p-toluene sulfonic acid. *Id.* at 15.

ii. Raf-Mediated Pathway

51. The Ras-Raf-MEK-ERK signaling transduction pathway is activated in response to growth factor stimulation and involves multiple proteins in the cell that communicate a signal from a

receptor on the cellular surface to the cellular nucleus, thereby activating transcription. Hembrook at 39-40; Rak at 265.

52. It was recognized by the late 1990s that many types of cancer share biochemical pathways, and dysregulation of such pathways may result in cancer. Buolamwini presents the Ras-MAP kinase pathway, shown below:



Id. at 501, Figure 1.

53. It was postulated that deviations from the proper progression of this pathway are often linked with cellular hyperproliferation associated with cancer. Regulation of this pathway was known to be a focus of research by the late 1990s, with investigators designing drugs and experiments to target the components of this signaling pathway. Buolamwini at 500.

54. Growth factors and mitogens use the Ras/Raf/MEK/ERK signaling transduction pathway to transmit signals from their receptors to intercellular molecules such as transcription

factors that can in turn induce or enhance gene expression. Some components of these pathways are mutated or aberrantly expressed in human cancer (e.g., Ras, B-Raf). Mutations also occur at genes encoding upstream receptors (e.g., EGFR and Flt-3). Rak, J. et al., "Oncogenes as inducers of tumor angiogenesis." *Cancer and Metastasis Reviews* 14:263-277, 1995; Buolamwini, John, "Novel anticancer drug discovery." *Current Opinion in Chemical Biology* 3:500-509, 1999; Hoshino, R., et al., "Constitutive activation of the 41-/43-kDa mitogen-activated protein kinase signaling pathway in human tumors." *Oncogenes* 18:813-822, 1999.

55. By the late 1990s, it was further known that tumors derived from the colon, pancreas, lung, and kidney frequently were associated with MAP kinase activation, particularly through the activation of Raf-1. Hoshino at 815-816, Table 4.

56. Moreover, as early as the mid-1990s, the role of the ras/raf signal transduction pathway in the regulation of VEGF expression in mouse embryo cells was well recognized, as was the role of p53 in tumorigenesis and its link to expression of VEGF (Kieser at 968). *See* Grugel, et al., "Both v-Ha-Ras and v-Raf Stimulate Expression of the Vascular Endothelial Growth Factor in NIH 3T3 Cells," *J. Biological Chem.* 270(43):25915-25918, 25918 (1995) ("Grugel"); Kieser, et al., "Mutant p53 potentiates protein kinase C induction of vascular endothelial growth factor expression," *Oncogene* 9:968 (1994) ("Kieser").

57. In 1995, Grugel postulated that "Ras as well as Raf are not only involved in cell proliferation and differentiation but also in tumor progression, mediated by increased expression of the tumor angiogenesis factor VEGF." Grugel at 25918. VEGFR-2 was known as a high affinity VEGF receptor tyrosine kinase. Ellis, et al., "Vascular Endothelial Growth Factor in Human Colon Cancer: Biology and Therapeutic Implications," *The Oncologist*, 5(suppl. 1):11-15 (February 2000)

(“Ellis”). As of the priority date, VEGFR was known to regulate angiogenesis and metastasis of bladder cancer. Karashima, et al., “Treatment of Human Metastatic Transitional Cell Carcinoma of the Bladder in a Murine Model with the Anti-Vascular Endothelial Growth Factor Receptor Monoclonal Antibody DC101 and Paclitaxel,” Clin. Cancer Research, 6: 2635-2643, 2635 (July 2000) (“Karashima”).

58. Substituted urea compounds mediated by raf kinase were known to be “useful in treating solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon)” with methods for administering preferred dosage amounts. WO 99/32106 (“Dumas”) at Abstract, 2:11-14, 27:20-30 (published on July 1, 1999). *See also* U.S. 2008/0269265 (“the ’265 Publication”) at [0003] (“useful in pharmaceutical compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase.”). The ’265 Publication also explicitly states that the “compounds of the invention are useful in treating solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder, or colon...” *Id.* The ’265 Publication further discloses a “method for the treatment of a cancerous cell growth” ([0020]), that the “daily oral dosage regimen will preferably be from 0.01 to 200 mg/kg of total body weight” ([0069]), along with various administration techniques for the recommended dose.

59. It later was postulated that sorafenib and sorafenib tosylate can be used to treat raf-mediated diseases, including carcinoma of the lung, pancreas, thyroid, bladder or colon in a human or animal in need. *See, e.g.,* U.S. Patent No. 8,124,630 (“the ’630 patent”) at Abstract, claims 1, 6, 8, 13. *See also* U.S. Patent App. Pub. No. 2003/0232765 to Carter et al. (“Carter”). Published on December 18, 2003, Carter discloses the tosylate salt of sorafenib. *Id.* at [0052]. Further, the

examples and experiments disclosed in Carter use sorafenib tosylate. *Id.* at [0091]. Carter also discusses the use of excipients in the formulation of aryl urea compounds as an oral dosage form. *Id.* at [0065]. The aryl urea compound may be combined with another chemotherapeutic agent that is a cytotoxic or cytostatic agent. *Id.* at [0038], [0048]. Carter also states that formulations of aryl urea compounds (e.g., sorafenib tosylate) may be used to treat diverse cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. *Id.* at [0036], [0045]. *See also* U.S. Patent No. 7,351,834 (“the ’834 patent”), disclosing sorafenib as useful for treating “human or animal solid cancer” and “raf mediated disease state in humans or mammals.” *Id.* at 1:55-2:14. Claim 41 is directed to: “A compound of claim 39 which is a tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N’-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea.” *Id.* at claim 41. I understand from Dr. Hollingsworth’s report that “N-(4-chloro-3-(trifluoromethyl)phenyl)-N’-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea” is a chemical name for sorafenib tosylate.” *See* Hollingsworth Op. Rep.

iii. p38-Mediated Pathway

60. The p38 mitogen-activate protein kinase (“p38 MAPK”) signal transduction pathway is activated as part of the inflammatory response in cells and also involves the phosphorylation of intracellular molecules. However, where the raf-mediated pathway is activated by growth factors, the p38 MAPK is activated by cellular stress factors (e.g., UV light and osmotic shock). *See e.g.*, Herlaar.

61. Stress factors use the p38 MAPK signal transduction pathway to transmit signals from their receptors to intracellular molecules such as transcription factors. It was known that p38 MAPK plays a key role in the activation of transcription factors affecting activity of certain tumor

suppressor genes. One such transcription factor, p53, was known to be the most frequently mutated gene in human cancers. Hannun at 78-80; Sanchez-Prieto, et. al., “A role for the p38 Mitogen-activated Protein Kinase Pathway in the Transcriptional Activation of p53 on Genotoxic Stress by Chemotherapeutic Agents,” *Cancer Research*, 50:2464-2472, 2471 (2000). Inhibition of p38 MAPK was known to diminish apoptosis.

iv. Diagnostic tests

62. As of 1999, knowledge regarding the in vivo angiogenic tumor pathways was fairly limited. In fact, the mere observation of a response in a tumor by, for example, blocking one pathway (such as one involving VEGF), does not allow a POSA to assume that there is no activity through another pathway (such as one involving p38).

63. Moreover, as of 1999, a clinician providing care for a patient with cancer was unaware of the specific drivers of tumor growth for a given tumor in a patient. Likewise, the treating physician was unaware of the precise mechanism by which a tumor responded to therapy. As such, clinical investigators who were developing novel therapies relied on knowledge of potential pathways by which cancer could proliferate and attempted to develop therapies that blocked those therapies.

64. At the time of invention, there was no existing commercial diagnostic test to differentiate or identify one particular pathway from another even assuming one pathway was mediating angiogenesis.

65. Even in the present day, it is unclear how one in practice could show in vivo, upon administration to a human, how a given drug compound operates within a particular pathway to treat a specific tumor.

Methods of Treating Tumors

i. Commonality Of Drug Treatment

66. As of 1999, the armamentarium of drugs available for the treatment of solid tumors like liver cancer and kidney cancer were limited and were characterized by low response rates and/or significant potential toxicity such that the risks of therapy exceeded the potential benefits for many patients. Because of the limited therapy options available for patients with kidney cancer and liver cancer, there was a significant desire to explore new treatments. Likewise, it was typical to examine and use drugs that had been approved in other cancers and apply them to the therapy of kidney cancer and liver cancer.

67. This was especially true given that knowledge of cancer biology in the late 1990s was sufficiently limited that only a few therapies designed to target specific pathways in cancer cells had been developed successfully. In fact, as of 1999, cancer was not considered to consist of the many hundreds of separate diseases as it is today.

68. As noted below, the agents used to treat kidney cancer and liver cancer were tested because they were effective in other types of cancer (e.g. breast cancer, lymphoma) and rarely were tested because they were felt to have a specific and unique rationale for therapy in kidney cancer or liver cancer.

ii. Therapy Modalities

69. Physicians who treat patients with cancer have three major modalities of therapy available: chemotherapy, surgery, radiation therapy. Surgical oncologists treat cancer patients through the resection of tumors. Radiation oncologists employ external beam radiation therapy or implanted radiation therapy to offer cytotoxic therapy to cancers. Medical oncologists employ

chemotherapy, biological therapy, and targeted therapy (such as monoclonal antibody-based therapies, kinase inhibitors, endocrine therapies) to cytoreduce cancer and potentially offer curative treatment to patients. Prior to 2000, the primary therapy available for medical oncology treatments was cytotoxic chemotherapy, in which the administered agents directly interfered with DNA or RNA replication. As cancer drugs that were developed and achieved FDA approval for specific cancer indications were often used off-label to treat other types of cancers. Freireich, E.J., “Societal Issues in Oncology: Regulatory Issues,” *Cancer Principles & Practices of Oncology* 5th ed. (DeVita, et al., eds. Lippincott-Raven), Ch. 57.2 (1997), at 2971-2972.

iii. Kidney Cancer

70. **Chemotherapy:** Chemotherapy was known to treat tumors by killing malignant cells or slowing their growth. Usually, the drugs worked by damaging the RNA or DNA responsible for instructing cell division and were most effective at killing cells that were rapidly dividing (i.e., triggering apoptosis). The chemotherapy available in 1999 and 2000 did not yield promising treatment responses for RCC. For example, Motzer (Motzer, R.J. & P. Russo, “Systemic Therapy for Renal Cell Carcinoma,” *J. Urology*, 163:408-417 (2002) (“Motzer”)) described single agent activity for vinblastine with a 3% response rate in data pooled from multiple trials. *Id.* at 409. Similarly, a trial conducted by Pyrhonen et al. in patients with metastatic renal cell carcinoma reported a 2% response rate for single agent Vinblastine. *Id.* at 411, Table 2. Vinblastine belongs to a class of chemotherapy drugs called alkaloids, which attack cells during various phases of division. Vinblastine works by inhibiting the microtubule structures within the cell, therein resulting in cell death. Similarly, response rates with 5-Fluorouracil and its derivatives were approximately 10%. *Id.* at 411. There was no convincing evidence that either of these agents extended survival for patients.

In essence, more than 90% of patients failed to achieve a meaningful response to cytotoxic chemotherapy.

71. **Cytokine Therapy:** Starting in the late 1980s, cytokines were considered the mainstay of treatment for locally advanced or metastatic RCC. RCC represents a potentially immunoresponsive malignancy in individual patients. Fossa, S.D., “Interferon in metastatic renal cell carcinoma,” *Semin. Oncol.*, 27(2):187-93 (Apr. 2000). Cytokines are messenger molecules that help control the growth and activity of immune system cells. Two types of cytokine agents, interferons and interleukin-2, have been the most evaluated of the cytokine therapy for treatment of RCC. Koneru, R. & S.J. Hotte, “Role of cytokine therapy for renal cell carcinoma in the era of targeted agents,” *Current Oncol.*, 16(Supl. 1):S40-S44 (2009).

72. **Interferon:** Interferons (INF) are naturally occurring glycoproteins that have strong antiviral activity and the ability to modulate immune response and cell proliferation. The antitumor activity of INF is mediated by various mechanisms—immunomodulation, antiproliferative activity, inhibition of angiogenesis, regulation of differentiation, interaction with growth factors, and modulation of gene expression, among others. *Id.* Motzer identified an overall response rate of 10% to single agent interferon and also indicated that this agent could extend survival as compared with chemotherapy.

73. **Interleukin-2 (IL-2):** IL-2 is a glycoprotein produced primarily by T-helper cells. Interaction of IL-2 with the IL-2 receptor, which is expressed in increased amounts on activator T cells¹, results in proliferation and differentiation of both B and T cells, cytotoxic cells, and

¹ A T-cell is a type of lymphocyte that plays a central role in cell-mediated immunity.

stimulation of a cascade of cytokines, including various interleukins, interferons, and tumor necrosis factors. The antitumor effect of IL-2 is mediated by its ability to stimulate and cause proliferation of natural killer cells (NK), lymphokine-activated killer cells (LAK), and other cytotoxic lymphocytes that attack tumor cells. Dutcher, J.P., “Current Status of Interleukin-2 Therapy for Metastatic Renal Cell Carcinoma and Metastatic Melanoma,” *Oncology* (Nov. 2002), available at: <http://www.cancernetwork.com/review-article/current-status-interleukin-2-therapy-metastatic-renal-cell-carcinoma-and-metastatic-melanoma>; Fishman, M. & J. Seigne, “Immunotherapy of Metastatic Renal Cell Cancer,” *Cancer Control*, 9(4):293-304 (2002). By 2000, it was known that there were occasional durable responses after high dose IL-2 therapy, but that the toxicity of the therapy was significant including hypotension, capillary leak syndrome, fevers, renal dysfunction, and pulmonary function. As such, this therapy was appropriate only for younger patients with excellent performance status and could not be used safely for the treatment of the majority of patients with renal cell cancer who were older and had co-morbid disease.

v. Liver Cancer

74. As of 2000, options available for the treatment of hepatocellular carcinoma (“HCC”) were extremely limited. A major conference was held in Barcelona in 2000 and experts met to review treatment options for hepatocellular cancer and issued recommendations regarding management. *See* Bruix, J., et al., “Clinical management of hepatocellular carcinoma. conclusions of the Barcelona-2000 EASL conference.” *Journal of Hepatology* 35: 421-430, 2001. For patients with advanced stage HCC, the expert panel concluded that there were no systemic chemotherapy agents that were recommended for use. Earlier studies had suggested some activity for Tamoxifen, an anti-estrogen, but this therapy subsequently was found to be inefficacious.

75. **Chemotherapy:** One form of chemotherapy available to treat hepatocellular cancer employed Adriamycin (doxorubicin). There are two proposed mechanisms by which doxorubicin acts in a tumor cell: (1) intercalation into DNA and disruption of topoisomerase-II-mediated DNA repair (triggering apoptosis) and (2) generation of free radicals with resultant damage to cellular membranes, DNA and proteins. Thorn, et al., “Doxorubicin pathways: pharmacodynamics and adverse effects,” *Pharmacogenet. Genomics*, 21(7):440-446 (2011), citing to Gewirtz, D.A., “A critical evaluation of the mechanisms of action proposed for the antitumor effects of the anthracycline antibiotics Adriamycin and daunorubicin,” *Biochem. Pharmacol.*, 57(7):727-41 (1991). Response rates to doxorubicin therapy in HCC were less than 10%. Carr, et al., “Hepatobiliary Cancers,” *Cancer Principles & Practice of Oncology*, 5th Ed. (DeVita, et al., eds., Lippincott-Raven), Ch. 32.5 (1997), at 1102-1103, Tables 32.5-11 and Table 32.5-12.

76. Another form of chemotherapy available to treat liver cancer involved the use of 5-fluoro-uracil. There are two proposed mechanisms by which 5-fluoro-uracil (5-FU) acts in a tumor cell: (1) by inhibiting essential biosynthetic processes, or (b) by being incorporated into macromolecules, such as DNA and RDA, and inhibiting their normal function. Langley, et al., “5-Fluorouracil: Mechanisms of Action and Clinical Strategies,” *Nature Reviews: Cancer*, 3:330-338 (2003). 5-FU is converted intracellularly to three main active metabolites (FdUMP, FdUTP, FUTP) that disrupt RNA synthesis and action of the nucleotide synthetic enzyme thymidylate synthase (TS). Carr at 1103, Table 32.5-12. An essential precursor for DNA biosynthesis – enzyme is critical for cancer chemotherapy. Rose, et al., “Thymidylate synthase: a critical target for cancer chemotherapy,” *Clin. Colorectal Cancer*, 1(4):220-229 (2002),

Dosing Regimen

77. A proper dosing regimen should indicate the amount to be administered to a human or animal, the frequency of dosing over any set timeline, or adjustments in dosing necessary based on certain patient groups. Indeed, the toxicity levels across species varies widely. *See, e.g.*, Boxenbaum, H. & C. DiLea, “First-time-in-Human Dose Selection: Allometric Thoughts and Perspectives,” *J. Clin. Pharmacol.*, 35:957-966, 958 (1995) (“Toxicity of substances varies among species. Some substances toxic to rats, for example, do not similarly affect other rodents or humans.”), *id.* at 965 (“drug dosage forms almost always differ between animal toxicity studies and human studies, and a poorly formulated dosage form used in toxicity studies may make the drug appear deceptively non-toxic in animals due to poor absorption... animal species may be generically more resistant to drug toxicity than humans. . . . No doubt other differences between humans and animal species could be posited, and this would further enhance the argument that a single algorithm for predicting human doses from animal experiments is fraught with difficulty.”)

78. Even among humans, the proper dosage can also be highly variable. Collins, J.M., “Pharmacology and Drug Development,” *J. National Cancer Institute*, 80(11):790-792, 791 (1988) (“Although there is a clear trend for clearances to be similar in mice and humans, there are important exceptions for individual drugs, based principally on differences in metabolic rates... In addition to deviations from general trends among species, there are also variations among individuals within a single species. . . . Some patients may experience more toxic effects than average, and others may derive less therapeutic benefit than average on account of differences in rates of clearance versus the population norm.”); Boxenbaum at 958 (noting highly varying results of toxicity depending on the allometry method used).

IV. LEGAL STANDARDS

Person of Ordinary Skill in the Art

79. Mylan's counsel has explained to me that many issues in patent law, including enablement, written description, anticipation, and obviousness, are determined from the perspective of a hypothetical person of ordinary skill in the art who is presumed to have known the relevant art at the time of the invention.

80. I understand from Mylan's counsel that several factors may be considered in determining the level of ordinary skill in the art, including: (1) the type of problems encountered in the prior art; (2) the solutions to those problems in the prior art; (3) the rapidity with which innovations are made; (4) the sophistication of the technology; and (5) the educational level of active workers in the field of the invention.

81. A "person of ordinary skill in the art" for purposes of this report, as of November 27, 2001, February 11, 2002, and September 29, 2004 which I understand to be the priority dates of the '330, '141, and the '933 patents, respectively, would have been an individual with a high level of education and skill, including an M.D. and/or a Ph.D. and at least two years of specialized experience in the area of treating solid tumors. The individual would have a substantive understanding of at least one of the following interdisciplinary fields: medicine, medicinal chemistry, pharmaceutical drug product development, organic chemistry, analytical chemistry, pharmacokinetics, biology, and any other related field.

82. I have been asked by counsel for Defendant to provide my expert opinion on the validity of the asserted claims, from the perspective of a POSA. My opinions as they relate to invalidity are the same under either the Defendant's or Plaintiffs' definition of a POSA.

Prior Art

83. Mylan's counsel has explained to me that prior art is what is known in the art at the time of the invention, i.e., as of the priority date of the patent. I understand from Mylan's counsel that a patent is entitled to a priority date that is as early as the date of its filing. Mylan's counsel has further explained to me that a patent may be entitled to the benefit of the filing date of an earlier application so long as certain legal criteria are met.

35 U.S.C. § 101 - Novelty

84. I understand from Mylan's counsel that, in order to be valid, the patented invention must meet a legal standard known as novelty, i.e., the patent claims must disclose a new process, machine, manufacture, or composition of matter, or any new improvement thereof.

35 U.S.C. § 102 – Anticipation

85. Mylan's counsel has explained to me that, in order to be valid, the patent claims that plaintiffs are asserting must not be anticipated by the prior art. I understand from Mylan's counsel that for a claim to be anticipated, it is necessary that a single prior art reference disclose each limitation of the claim, either expressly or inherently. Mylan's counsel has further explained to me that a claim limitation not expressly found in a reference may nonetheless be inherent if the art described in the reference necessarily functions in accordance with, or includes, the claimed limitations.

35 U.S.C. § 103 – Obviousness

86. Mylan's counsel has explained to me that a patent is invalid where the differences between the patent claims and the prior art are such that the claimed invention, as a whole, would have been obvious to a person of ordinary skill in the art at the time of the invention. In analyzing

the question of obviousness, I have been asked by Mylan's counsel to consider the following: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; and (3) the level of skill in the prior art.

87. I understand from Mylan's counsel that a claim may be obvious if it is a predictable improvement or combination of prior art elements according to their established functions. Mylan's counsel has explained to me that a combination of prior art elements is predictable where the prior art provides teaching, suggestion, or motivation to combine the references in such a way as to give a person of ordinary skill in the art a reasonable expectation of success in arriving at the claimed subject matter.

88. I understand from Mylan's counsel that in determining what would have been obvious, I may take into account the inferences and ordinary creativity that a person of ordinary skill in the art would employ.

i. Obviousness-Type Double Patenting

89. Mylan's counsel has explained to me that an applicant cannot obtain a second patent on a claim that is deemed an obvious variation of another first patent; otherwise, the patent claim fails for obviousness-type double patenting. I understand from Mylan's counsel that the purpose of this restriction is to prevent an unjustified and improper extension of the right to exclude granted by a patent.

35 U.S.C. § 112

90. Mylan's counsel has explained to me that, in order to be valid, the patent claims that plaintiffs are asserting must meet a legal standard known as enablement. I understand from Mylan's counsel that the enablement standard requires the patent's specification to describe to a person of

ordinary skill in the art how to make and use the full scope of the claimed invention without undue experimentation. Mylan's counsel has explained to me that whether a patent's disclosure would require "undue experimentation" will depend on the facts particular to that patent. Using the example of the present case, in which the patents address the intersection of two complex fields—medicinal chemistry and medical oncology—I understand from Mylan's counsel that the patent will need to include more working examples than would a patent dealing with a less complex subject matter, such as a patent claiming a single compound or the use of a single compound to treat a single disease.

91. I understand from Mylan's counsel that plaintiffs' patents must also meet a separate legal standard known as the written description requirement. Mylan's counsel has explained that, in order to meet this standard, the patent's specification must describe the claimed invention in such a way that a person of ordinary skill in the art would understand that the inventors actually invented what is claimed. Mylan's counsel has explained that this standard is often described in terms of "possession" of the invention. I understand from Mylan's counsel that in order to show possession of the invention, the specification must describe an invention that a person of ordinary skill in the art would understand, and it must also show that the inventor actually invented the claimed invention as of the filing date. I also understand that, as with the enablement standard, the question of whether a patent's written description is sufficient will depend on the context of the case, but that a description that merely makes the invention obvious or describes only a starting point for further research will not meet the standard.

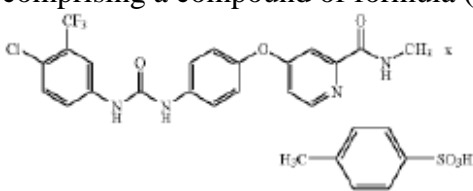
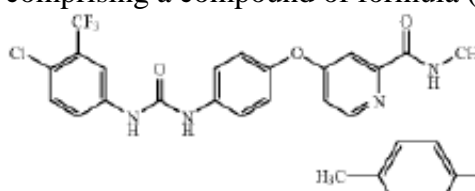
92. I understand from Mylan's counsel that the patent claims that plaintiffs are asserting must additionally meet a separate legal standard known as the definiteness requirement. Mylan's

counsel has explained that, in order to meet this requirement, the asserted claims must clearly and precisely inform a person of ordinary skill in the art of the boundaries of the protected subject matter so as to be informed of what constitutes infringement. I understand from Mylan's counsel that where a claim fails to meet this requirement, the patent is invalid for indefiniteness.

93. Mylan's counsel has explained to me that a patent claim is also invalid for indefiniteness where the claim contains no earlier recitation or limitation of the claimed subject matter and where it would be unclear as to what element the limitation was making reference. I understand from Mylan's counsel that such a patent claim is invalid for lack of antecedent basis.

V. CLAIM CONSTRUCTION

94. I understand that the parties have agreed upon the following constructions for certain claim construction terms and/or phrases:

Claim	Term	Parties' Agreed Upon Construction
'141 patent: 7	A method of blocking angiogenesis in a tumor of the kidney	This phrase is limiting
'141 patent: 8, 9	the tumor of the kidney that is treated	the tumor of the kidney that is the subject of the method of blocking angiogenesis
'141 patent: 8, 9	hyperpermiability processes	processes associated with high permeability of blood vessels
'933 patent: 8	A pharmaceutical composition comprising a compound of formula (I) 	A pharmaceutical composition comprising a compound of formula (I)  wherein the compound of formula (I) in

Claim	Term	Parties' Agreed Upon Construction
	substantially in the polymorph I form	the composition is largely, but not necessarily wholly, in the polymorph I form
'933 patent: 1, 2, 8,16, 28-29	peak maxima of the 2 theta angle [peak information]	peak maxima of the 2 theta angle [peak information] ± 0.2

VI. INVALIDITY OPINIONS

Invalidity of the '141 Patent

95. The '141 patent issued on December 31, 2013 from Application No. 13/551,884, filed on July 18, 2012. The '141 patent was filed from Provisional Application No. 60/354,950, filed on February 11, 2002.

i. The Asserted Claims of the '141 Patent

96. Claim 7 of the '141 patent recites a method of blocking tumor angiogenesis in a tumor of the kidney comprising administering to a human or other mammal with a tumor of the kidney an effective amount of the tosylate salt of sorafenib.

97. Claim 8 of the '141 patent, which depends from claim 7, further includes the limitation that the tumor of the kidney that is treated is characterized by abnormal angiogenesis or hyperpermeability processes, which are not raf-mediated nor p38-mediated.

98. Claim 9 of the '141 patent depends from claim 8, and further includes the limitation that the tumor of the kidney that is treated is characterized by abnormal angiogenesis or hyperpermeability processes, which are mediated by KDR (VEGFR-2).

ii. Claims 7-9 of the '141 Patent Are Anticipated by the Prior Art

99. WO 00/42012 (“the '012 application”) was published in July 20, 2000, and thus qualifies as 35 U.S.C. § 102(b) prior art to the '141 patent, with a priority date of February 11, 2002. It is my opinion that the '012 application discloses each and every element of the method recited in claims 7-9 of the '141 patent, either expressly or inherently, and thus anticipates these claims.

100. Specifically, the '012 application identifies sorafenib tosylate as a chemotherapeutic agent that could be administered orally to patients suffering from solid tumors, providing non-limiting examples of lung, pancreas, thyroid, bladder, and colon tumors. *Id.* at 2:18-29. The '012 application further discloses that sorafenib inhibits raf kinase. *See id.* at abstract, 2:10-14. Lastly, the '012 application discloses a daily oral dosage for administration of the compound listed of between 0.01 and 200 mg/kg of sorafenib. *Id.* at 12:21-32.

101. Additionally, by the time of the filing of the '141 patent, it was known that tumor angiogenesis was a “prerequisite” for the substantive growth of tumors. *See* '141 patent at 2:1-2. Sorafenib’s biochemical property of blocking tumor angiogenesis through KDR (VEGFR-2) inhibition as disclosed in the '141 patent is an inherent property. Thus, sorafenib would “block tumor angiogenesis” every time that sorafenib is used to treat a tumor in a patient.

102. It is my opinion that Claim 7 of the '141 patent claims the exact method disclosed in the '012 publication. As noted above, Claim 7 of the '141 patent discloses the administration of sorafenib tosylate to patients with a tumor of the kidney, which a POSA would have known to be a solid tumor. The natural and inherent result of that method is the inhibition of tumor angiogenesis. Further, the '012 publication provides an effective amount to be used as between 0.01 and 200 mg/kg of sorafenib.

103. As discussed above, the natural and inherent results of the method disclosed in claim 7 of the '141 patent is the inhibition of tumor growth by inhibition of Raf kinase and the inhibition of KDR (VEGFR-2) activity. Accordingly, it is my opinion that claims 8 and 9 of the '141 patent disclose limitations that are inherently anticipated by the '012 application.

104. For at least these reasons, it is my opinion that claims 7-9 of the '141 patent are invalid as anticipated by at least the '012 application under 35 U.S.C. § 102(b).

iii. Claims 7-9 of the '141 Patent Would Have Been Obvious to a Person of Ordinary Skill in the Art at the Time of Invention

105. To the extent each limitation of claims 7-9 of the '141 patent are not expressly or inherently disclosed in the '012 application, it is my opinion that claims 7-9 of the '141 are obvious in view of the prior art available at the time of the invention.

1. Claim 7 the '141 Patent Would Have Been Obvious to a Person of Skill in the Art Over the '012 Publication, In View of Hoshino

106. Hoshino was published in January 1999, and thus qualifies as prior art to the '141 patent, with a priority date of February 11, 2002. It is my opinion that claim 7 of the '141 patent would have been obvious to a person of ordinary skill in the art over the '012 publication, in view of Hoshino.

107. As discussed above, following the disclosure provided in the '012 application, a person of ordinary skill in the art would have known that sorafenib could be administered to patients having solid tumors and would have a reference for the effective amount to be administered. From the same disclosure, a POSA would also know that sorafenib could be formulated as a tosylate salt for oral administration. Further, the '012 application discloses that such compounds are useful in pharmaceutical compositions from human use "in the treatment of tumors and/or cancerous cell growth mediated by raf kinase." *Id.* at 2:10-15. As such, a POSA, who would be an experienced

scientist familiar with medicinal chemistry, biochemical pathways involved with cancer, and anti-cancer therapies, would recognize that sorafenib tosylate may be an effective treatment of any cancer in which raf was implicated.

108. Hoshino identifies kidney cancer as one such cancer in which aberrant activity of raf kinase is implicated. Hoshino at 815. Specifically, Hoshino shows that MAP kinases are overactive in human kidney tumors. *Id.* Hoshino also demonstrates that MEK and raf activation are responsible for that elevated MAP kinase activity. *Id.* at 815-16; Table 4.

109. It is my opinion that if one skilled in the art knew sorafenib was an inhibitor of raf and effective in treating solid tumors from the '012 application, it would have been obvious to employ sorafenib in the treatment of kidney tumors (a type of solid tumor). Thus, it is my opinion that claim 7 provides a predictable result of that taught in the '012 application and Hoshino, combined.

110. For at least these reasons, it is my opinion that claim 7 of the '141 patent is invalid as obvious under 35 U.S.C. § 103(a) over the '012 application in view of Hoshino.

2. Claims 7-9 of the '141 Patent Would Have Been Obvious to a Person of Skill in the Art Over the '012 Publication, In View of Buolamwini

104. Buolamwini was published in August 1999, and thus qualifies as prior art to the '141 patent, with a priority date of February 11, 2002. It is my opinion that claims 7-9 of the '141 patent would have been obvious to a person of ordinary skill in the art over '012 publication, in view of Buolamwini.

105. As indicated above, it is my opinion that Claim 7 of the '141 patent claims the same method disclosed in the '012 publication. It is further my opinion that a person of ordinary skill in the art would have known that sorafenib could be administered to patients having solid tumors and

would have a reference for the effective amount to be administered, as detailed above. From the same disclosure, it is my opinion that a person of ordinary skill in the art would also have known that sorafenib could be formulated as a tosylate salt for oral administration.

106. Based upon the disclosure provided in the '012 application, it is my opinion that a person of ordinary skill in the art would have known that the inhibition of abnormal angiogenesis mediated by KDR (VEGFR-2) is a natural outcome of the administration of sorafenib, as detailed above.

107. Buolamwini further discloses that raf kinase is implicated in tumor growth both directly and indirectly through angiogenesis via the VEGFR receptor. *See* Buolamwini at 501-504.

108. Considering the '012 application in light of Buolamwini, it is my opinion that a person of skill in the art would have known that raf kinase is activated with KDR (VEGFR-2)-mediated tumor angiogenesis and that sorafenib inhibited raf kinase. Thus, it is my opinion that a person of ordinary skill in the art would have known that administration of sorafenib would be an effective treatment for solid tumors, such as kidney tumors.

109. Accordingly, it is my opinion that it would have been obvious for one of ordinary skill in the art to combine the teachings of the '012 application and Buolamwini and use sorafenib to block KDR (VEGFR-2)-mediated angiogenesis by inhibiting raf—an enzyme known to be involved in VEGF's angiogenic effects.

110. For at least these reasons, it is my opinion that claims 7-9 of the '141 patent are invalid as obvious under 35 U.S.C. § 103(a) over the '012 application in view of Buolamwini.

3. Claims 7-9 of the '141 Patent Would Have Been Obvious to a Person of Skill in the Art Over the '012 Publication, In View of Grugel, Kieser, Ellis, or Karashima.

112. As discussed above, by the time of the filing of the application that lead to the '141 patent, the method of treating patients with tumors by administration of sorafenib tosylate was known. '012 Publication at 2. The effects of the ras/raf signal transduction pathway on the regulation of VEGF expression in mouse embryo cells was known. Grugel at 25918. As of 1994, the role of p53 in tumorigenesis and its link to expression of VEGF was also known. *See* Kieser at 968. VEGFR-2 was known as a high affinity VEGF receptor tyrosine kinase, and VEGFR was known to regulate angiogenesis and metastasis of bladder cancer. Ellis at 11-15; Karashima at 2635.

113. Thus, as of the priority date, a POSA would have been motivated to treat kidney tumors characterized by abnormal angiogenesis and hyperpermiability processes mediated by the VEGFR-2-pathway using a drug known to inhibit the raf kinase pathway in other solid cancers. *See* '012 Publication at 2. Accordingly, each claims 7-9 of the '141 patent are obvious in view of the prior art discussed above.

4. Claims 7-9 of the '141 Patent Would Have Been Obvious to a Person of Skill in the Art Over the '012 Publication, In View of Rudin

112. It is my opinion that claims 7-9 of the '141 patent would have been obvious to a person of ordinary skill in the art over the '012 publication, in view of Rudin, C., et al., "Phase I Trial of ISIS 5132, an Antisense Oligonucleotide Inhibitor of *c-raf-1*, Administered by 24-hour Weekly Infusion to Patients with Advanced Cancer." *Clinical Cancer Research* 7: 1214-1220, 2001 ("Rudin").

113. Rudin relates to the findings of Phase I trials that were presented in 1998, and thus qualifies as prior art to the '141 patent, with a priority date of February 11, 2002. Rudin relates to a

presentation delivered in 1998 regarding the phase I clinical trial for ISIS 5132, a specific antisense oligonucleotide for the *raf1* gene, tumors of the kidney was considered a viable target for sorafenib tosylate. *See* “Isis Presentations at ASCO Show Antitumour Activity of Antisense Cancer Drugs; Meeting Highlights Antisense Mechanism,” Isis Pharmaceuticals Press Release (May 19, 1998); O’Dwyer, et al., “Phase I/ Pharmacokinetic/ Pharmacodynamic Trial of Raf-1 Antisense ODN (ISIS 5132, CGP 69846A),” *Am. Soc. Clin. Oncology*, 17:210a (1998); Holmlund, et al. “Phase I Trial of *C-raf* Antisense Oligonucleotide ISIS 5132 (CGP 69846A) by 21-Day Continuous Intravenous Infusion (CIV) in Patients with Advanced Cancer,” *Am. Soc. Clin. Oncology*, 17:210a (1998). Rudin discloses that tumors of the kidney are likely to be treated by sorafenib or sorafenib tosylate.

114. Further, the applicable tools and techniques for investigating whether a drug is effective for various tumors were available and regularly practiced by those in the field prior to the time of invention. In fact, during the prosecution of the ’330 patent, in response to a rejection from the PTO on the basis that the patent specification does not enable treatment of a variety of tumors, the applicant argued that “[t]reating a particular tumor based on this disclosure would at most involve routine experimentation for one of ordinary skill in the art as is clearly evidenced by the clinical trials open to patients with unspecified solid tumors.” June 20, 2012 Non-Final Rejection; December 20, 2012 Applicant Arguments/Remarks at 2, 4. *See also* September 17, 2013 Applicant Arguments/Remarks at 4-6 (“sufficient evidence of the broad application of raf kinase inhibitors in treating tumors. . . . Clearly it was known in the art prior to this invention that kinase inhibitors, such as ISIS 5132 and those disclosed in this application, find use in treating a wide variety of solid tumors.”).

115. Considering the disclosure provided in the '012 publication, it is my opinion that a person of ordinary skill in the art would have known that sorafenib could be administered to patients having solid tumors and would have a reference for the effective amount to be administered, as detailed above. From the same disclosure, it is my opinion that a person of ordinary skill in the art would also have known that sorafenib could be formulated as a tosylate salt for oral administration.

116. Claims 7-9 of the '141 patent are directed to methods of blocking angiogenesis or treating a tumor of the kidney. The additional elements of the pathways used to block angiogenesis are inherent in this method, as discussed above. Accordingly, it is my opinion that it would have been obvious for one of ordinary skill in the art to combine the teachings of the '012 application and Rudin and use sorafenib to treat tumors of the kidney.

117. For at least these reasons, it is my opinion that claims 7-9 of the '141 patent are invalid as obvious under 35 U.S.C. § 103(a) over the '012 application, in view of Rudin.

4. The Asserted Claims of the '141 Patent Are Obvious Over the '012 Publication, In View of Rak

118. Rak was published in 1995, and thus qualifies as prior art to the '141 patent, with a priority date of February 11, 2002. It is my opinion that claims 7-9 of the '141 patent would have been obvious to a person of ordinary skill in the art over '012 publication, in view of Rak, would have been obvious to a person of ordinary skill in the art at the time of the invention.

119. Following the disclosure provided in the '012 publication, it is my opinion that a person of ordinary skill in the art would have known that sorafenib could be administered to patients having solid tumors and would have a reference for the effective amount to be administered, as detailed above. From the same disclosure, it is my opinion that a person of ordinary skill in the art would also have known that sorafenib could be formulated as a tosylate salt for oral administration.

120. Rak further discloses that angiogenesis is related to ras-raf-MAP kinase signal transduction and that angiogenesis was directly related to KDR (VEGFR-2) mediation. *See* Rak at 264-270 and Supplemental Contentions for the '141 and '330 Patents. It is my opinion that once it was established that sorafenib was a raf inhibitor (as disclosed in the '012 publication), a person of ordinary skill in the art would have considered it obvious that sorafenib would have anti-angiogenesis properties.

121. It is also my opinion that even if it were not known that raf inhibition was related to blocking angiogenesis, it would have been routine for a person of ordinary skill in the art to perform the experiments necessary to come to this finding. *See, e.g.,* '141 Patent Prosecution May 2, 2013 Applicant Arguments/Remarks at 8 (in regards to the “claimed aspect of blocking tumor angiogenesis using the claimed compounds,” “routine assay techniques can be used to test the anti-angiogenic activity of the claimed molecules at the cellular and physiological level.”).

122. Claims 7-9 of the '141 patent are directed to methods of blocking angiogenesis or treating a tumor of the kidney. The additional elements of the pathways used to block angiogenesis are inherent in this method, as discussed above. Accordingly, it is my opinion that it would have been obvious for one of ordinary skill in the art to combine the teachings of the '012 application and Rak and use sorafenib to treat tumors of the kidney.

123. For at least these reasons, it is my opinion that claims 7-9 of the '141 patent are invalid as obvious under 35 U.S.C. § 103(a) over the '012 application, in view of Rak.

5. Claims 7-9 of the '141 Patent Are Obvious Over the '012 Publication, In View of Rak

124. By the early 2000s, the method of treating patients with tumors by administration of sorafenib tosylate was known. '012 Publication at 2. Thus, as of the priority date, a POSA would

have been motivated to treat kidney tumors characterized by abnormal angiogenesis and hyperpermiability processes mediated by the VEGFR-2-pathway using a drug known to inhibit the raf kinase pathway in other solid cancers. *See* '012 Publication at 2.

125. Accordingly, each of the Asserted Claims of the '141 patent are obvious in view of the prior art discussed above.

v. Claims 7-9 are Invalid for Obviousness-Type Double Patenting

1. Previously filed U.S. Patent No. 8,841,330

126. It is my opinion that claims 7-9 of the '141 patent are obvious variations of claims 1, 7, 13, and 14 of the '330 patent. Claim 1 of the '330 patent recites a method for the treatment of a tumor of the prostate, breast, liver, ovary or cervix in a human or animal comprising administering an effective amount of sorafenib or a pharmaceutically acceptable salt thereof. Claim 7 of the '330 patent claims the same method as claim 1, but uses the tosylate salt of sorafenib. Claims 13 and 14 of the '330 patent are similar to the claims 1 and 7 respectively, except claims 13 and 14 are limited to the treatment of liver cancer.

127. It is my opinion that claims 7-9 of the '141 patent are invalid under the doctrine of obviousness-type double patenting because the differences between the claims 7-9 of the '141 patent and the claims of the '330 patent are not patentably distinct. The '141 patent merely claims an inherent and/or obvious variant of the '330 claims—treating kidney tumors. Treating kidney tumors is inherent and/or an obvious variant of the '330 patent because as mentioned above, treating KDR-mediated tumors is a natural outcome of administering sorafenib in an “effective amount.”

2. Previously filed U.S. Patent No. 8,124,630

128. It is my opinion that claims 7-9 are also obvious variations of claims 1, 6, 8, and 13 of the '630 patent. Claim 1 of the '630 patent recites a “method for treatment of carcinoma of the lung, pancreas, thyroid, bladder or colon in a human or animal in need thereof comprising administering an effective amount of [sorafenib] . . . or a pharmaceutically acceptable salt thereof.” *Id.* at 93:52-94:14. Claim 6 depends from claim 1 and claims a method for the treatment of carcinoma of the bladder in a human in need thereof. Claim 8 mirrors claim 1 using the tosylate salt of [sorafenib]. Claim 13 depends from claim 8 and claims a method for the treatment of carcinoma of the bladder.

129. It is my opinion that, similar to the analysis above with respect to the '330 patent, claims 1, 6, 8, and 13 of the '630 patent render claims 7-9 of the '141 patent invalid under the doctrine of obviousness-type double patenting.

vi. The Specification of the '141 Patent Does Not Enable a Person of Ordinary Skill in the Art to Practice the Invention without Undue Experimentation

130. It is my opinion that the specification of the '141 patent does not describe to a person of ordinary skill in the art how to make and use the full scope of claims 7-9 without undue experimentation.

131. Claim 7 includes the limitation of “administering . . . an effective amount” of the tosylate salt of sorafenib. *Id.* at 40:42-63. Claims 8 and 9, which depend on claim 7, incorporate this limitation by virtue of their being dependent claims.

132. It is my opinion that the specification of the '141 patent fails to disclose a manner and process of “administering . . . an effective amount” in “full, clear, and concise, and exact terms” as to enable a person of skill in the art to practice the invention because he or she is not given guidance on at least the following necessary information: (1) how much sorafenib to administer to a human or

animal each time; (2) how often to administer sorafenib tosylate over any timeline; or (3) the adjustments in dosing necessary based on renal function. *See* Boxembaum at 958 and 965; Collins at 791.

133. It is also my opinion that the specifications of the '141 patent fails to disclose a manner and process of “administering . . . an effective amount” in “full, clear, and concise, and exact terms” as to enable a person of ordinary skill in the art to practice the invention based solely on the disclosed range of 0.01 mg/kg – 200 mg/kg, which constitutes a difference in magnitude of 20,000-fold. '141 patent at 9:42-49. For example, for an average male with a weight of 70 kg, this dosing range translates to a dose between 7 mg to 14 g, and would require extensive studies to determine the appropriate amount to administer to the individual. Further, it is my understanding that it was known in the prior art that such generalized dosing guidelines can be highly inaccurate and that allometric calculations, when spread across various species can be highly variable, and lead to rapid toxicity. *See* Boxembaum at 958 and 965; Collins at 791.

134. For at least these reasons, it is my opinion that claims 7-9 of the '141 patent are invalid under 35 U.S.C. § 112 for lack of enablement.

vii. The Specification of the '141 Patent Lacks Sufficient Written Description

135. It is my opinion that the specification of the '141 patent does not describe claims 7-9 in such a way that a person of ordinary skill in the art would understand that the inventors actually invented what is claimed.

136. Claim 8 of the '141 patent depends on claim 7 and include the limitation that the tumor of the kidney that is treated is characterized by “abnormal angiogenesis or hyperpermeability

processes, which are not raf-mediated nor p38-mediated.” *Id.* at 40:64-67. Claim 9 of the ’141 patent depends on claim 8 and as such also includes the same limitation.

137. It is my opinion that the specification of the ’141 patent fails to describe “abnormal angiogenesis or hyperpermiability processes that are not raf-mediated or p38-mediated.” In fact, the ’141 patent does not contain any description of tumors that possess “abnormal angiogenesis or hyperpermiability processes that are not p38-mediated or raf-mediated.” The ’141 patent mentions raf- and p38-mediated processes only once outside of the claims. *See id.* at 9:60- 10:11 (restating claims 4, 5, and 8 as “another embodiment of the invention”).

138. The specification does not identify any tumors that possess abnormal angiogenesis or hyperpermiability processes that are not raf- or p-38 mediated. The specification also does not provide any examples of cancerous biochemical processes that may lead to abnormal angiogenesis or hyperpermiability processes without activation of raf or p38.

139. The totality of the ’141 patent’s substantive description on the biochemical effects of sorafenib are contained in three “Biological Examples.” *Id.* at 25:43- 39:52. The first is a cell-free assay of sorafenib’s inhibition of KDR kinase. *Id.* at 25:45- 26:33. The second is a prophetic cellular in vitro assay of inhibition of KDR kinase in NIH3T3 cells by sorafenib, for which no results are reported. *Id.* at 38:8-58. The third is a prophetic cellular in vivo assay of inhibition of sorafenib’s anti-angiogenesis effects to be conducted using an implant of human tumor cells formulated in vitro in mice, for which no results are reported. *Id.* at 38:59- 39:52.

140. It is my opinion that none of that disclosure supports a claim directed to methods of inhibiting angiogenesis where the processes are not raf- or p38-mediated. It is also my opinion that

the '141 patent further lacks any scientific data or substantive discussion of any such angiogenic processes.

141. For at least these reasons, it is my opinion that claims 7-9 of the '141 patent are invalid under 35 U.S.C. § 112 for lack of written description.

viii. Claims 8-9 of the '141 Patent Are Indefinite

142. It is my opinion that claims 8-9 of the '141 patent do not clearly and precisely inform a person of ordinary skill in the art of the boundaries of the protected subject matter so as to be informed of what constitutes infringement.

143. Claims 8 and 9 of the '141 patent include the phrase “hyperpermiability processes.” It is my opinion that the specification of the '141 patent fails to adequately define “hyperpermiability processes.” In fact, the specification of the '141 patent does not define “hyperpermiability processes” at all. In my opinion, this phrase would not be readily familiar to a person of ordinary skill in the art.

144. For these reasons, it is my opinion that claims 8-9 of the '141 patent are invalid under 35 U.S.C. § 112 as indefinite.

ix. Claims 8-9 of the '141 Patent Lack Antecedent Basis

145. It is my opinion that claims 8-9 of the '141 patent do not contain earlier recitation or limitation of the claimed subject matter therein and that it would be unclear as to what element the limitation was making reference.

146. Claim 8 of the '141 patent depends on claim 7, which discloses “a method of blocking angiogenesis in a tumor of a kidney comprising administering to a human or other mammal with a tumor of the kidney an effective amount of the tosylate salt of [sorafenib].” *Id.* at 40:42-63.

Conversely, Claim 8 discloses “wherein the tumor of *the kidney that is treated* is characterized by abnormal angiogenesis or hyperpermeability processes. . .” *Id.* at 40:64-67 (emphasis added). Claim 7 never recites a tumor of the kidney “that is treated,” thus, claim 8 lacks antecedent basis. Claim 9 depends from claim 8, thus claim 9 suffers a similar fate.

147. For at least these reasons, it is my opinion that claims 8-9 of the ’141 patent are invalid for lack of antecedent basis.

x. Claim 7-9 of the ’141 Patent Do Not Disclose Novel Processes

148. It is my opinion that claims 8-9 of the ’141 patent do not disclose a new process, machine, manufacture, or composition of matter, or any new improvement thereof.

149. As discussed above, claims 7-9 merely describe the mechanism of action by which sorafenib acts in the method of treatment. Disclosing the specific pathways or mechanism in which sorafenib operates does not render the invention any more “new” or “useful” than the prior art.

150. For at least these reasons, it is my opinion that claims 7-9 of the ’141 patent are invalid under 35 U.S.C. § 101 for lack of novelty.

Invalidity of the ’330 Patent

151. I understand that Plaintiffs contend that the claimed subject matter of the ’330 patent was invented no later than January 13, 1999. Regardless of whether this invention date has been properly established, my opinion as provided in this report would be equally applicable to this contended invention date.

i. The Asserted Claims of the ’330 Patent

152. Claim 4 of the ’330 patent depends on non-asserted claim 1. Claim 1 of the ’330 patent recites a method of treating a tumor of the prostate, breast, liver, ovary or cervix in a human

or animal comprising administering an effective amount of sorafenib or a pharmaceutically acceptable salt thereof. Claim 4 further includes the limitation that the tumor is of the liver.

153. Claim 10 of the '330 patent depends on non-asserted claim 7. Claim 7 of the '330 patent recites a method treating a tumor of the prostate breast, liver, ovary or cervix in a human or animal comprising administering an effective amount of a tosylate salt of sorafenib. Claim 10 further includes a limitation that the tumor is of the liver

154. Claim 13 of the '330 patent recites a method for treating a tumor of the liver in a human or animal in need thereof comprising administering an effective amount of sorafenib or a pharmaceutically acceptable salt thereof.

155. Claim 14 of the '330 patent, which depends from claim 13, further requires that the tosylate salt of sorafenib be administered.

ii. Claims 4, 10, 13, and 14 of the '330 Patent Would Have Been Obvious to a Person of Ordinary Skill in the Art at the Time of Invention

156. It is my opinion that claims 4, 10, 13, and 14 of the '330 patent are obvious in view of the prior art available at the time of the invention.

157. In forming my opinions, I have reviewed the findings of Dr. Bihovsky's opening expert report, and understand that it his opinion that sorafenib and sorafenib tosylate are obvious in light of the prior art. Since claims 4, 10, 13, and 14 of the '330 patent claim sorafenib or its tosylate salt, this element of each of the '330 Asserted Claims is not novel or is obvious. Accordingly, I incorporate by reference the arguments set forth above for the '576 patent, the '834 patent, and the '623 patent from Dr. Bihovsky's Opening Expert Report.

1. Claims 4, 10, 13, And 14 Of The '330 Patent Would Have Been Obvious Over The '265 Publication In View Of Dumas

158. As described above, the '265 Publication describes administering substituted diphenyl ureas useful for the treatment of a cancerous cell growth mediated by raf kinase, where the use of such compounds are “useful in pharmaceutical compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase” and are “useful in treating solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder, or colon” 265 Publication at [0003], [0020]. It also discloses that the “daily oral dosage regimen will be preferably be from 0.01 to 200 mg/kg of total body weight, thereby discloses the “effective amount” of claims 1 and 13. *Id.* at [0069].

159. Dumas discloses “[m]ethods of treating tumors mediated by raf kinase, with substituted urea compounds.” Dumas at Abstract. In particular, it teaches that such compounds are “useful in treating solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon).” Dumas at 2:11-14. Like the '265 Publication, Dumas also provides methods for administering and preferred dosage amounts. *Id.* at 27:20-30.

160. Each and every claim limitation of the '330 patent is met by both Dumas and the '265 Publication as discussed above. Thus, Asserted Claims 4, 10, 13, and 14 of the '330 patent are invalid as obvious over the '265 Publication or Dumas alone or in combination with one another.

2. Claims 4, 10, 13, and 14 of the '330 Patent Would Have Been Obvious Over Rudin

161. As indicated above, the presentation that Rudin relies on in his publication was delivered in 1998, and thus qualifies as prior art to the '330 patent, with a priority date as early as January 13, 1999.

162. It is my opinion that claims 4, 10, 13, and 14 of the '330 patent would have been obvious to a person of ordinary skill in the art over the disclosure in Rudin.

163. As discussed above, Rudin discloses that tumors of the liver are likely to be treated by sorafenib or sorafenib tosylate. Specifically, Rudin recounts a presentation delivered in 1998 regarding the phase I clinical trial for ISIS 5132, a specific antisense oligonucleotide for the *raf l* gene. As such, it follows that tumors of the liver were considered a viable target for sorafenib tosylate. *See* Rubin at 1216-1217.

164. As discussed above, the applicable tools and techniques for investigating whether a drug is effective for various tumors were available and regularly practiced by those in the field prior to the time of invention.

165. Claims 4, 10, 13, and 14 of '330 patent are directed to a method for treating a tumor of the prostate, breast, liver, ovary, or cervix, or a method of treating liver cancer by administering an effective amount of sorafenib or a pharmaceutically acceptable salt thereof. Accordingly, it is my opinion that it would have been obvious for one of ordinary skill in the art, in considering the teachings of Rudin, to use sorafenib to treat tumors of the liver and further to use the tools and techniques available to investigate sorafenib's effectiveness to use sorafenib to treat the tumors of the prostate, breast, ovary, or cervix.

166. For at least these reasons, it is my opinion that claims 1, 4, 7, 10, and 13 of the '330 patent are invalid as obvious under 35 U.S.C. § 103(a) in view of Rudin.

iii. The Specification of the '330 Patent Does Not Enable a Person of Ordinary Skill in the Art to Practice the Invention without Undue Experimentation

167. It is my opinion that the specification of the '330 patent does not describe to a person of ordinary skill in the art how to make and use the full scope of claims 4, 10, 13, and 14 without undue experimentation.

168. Claims 1, 7, 13 of the '330 patent include the limitation of “administering . . . an effective amount” of the tosylate salt of sorafenib. Claims 4, 10, and 14, which depend from claims 1, 7, and 13 respectively, incorporate this limitation by virtue of their being dependent claims.

169. It is my opinion that the specification of the '330 patent fails to disclose a manner and process of “administering . . . an effective amount” in “full, clear, and concise, and exact terms” as to enable a person of skill in the art to practice the invention because he or she is not given guidance on at least the following necessary information: (1) how much sorafenib to administer to a human or animal each time; (2) how often to administer sorafenib tosylate over any timeline; or (3) the adjustments in dosing necessary based on hepatic or renal function.

170. It is also my opinion that the specifications of the '330 patent fails to disclose a manner and process of “administering . . . an effective amount” in “full, clear, and concise, and exact terms” as to enable a person of ordinary skill in the art to practice the invention additionally because the '330 patent only discloses the way in which sorafenib tosylate operates through the inhibition of raf. There is no specific dosing schedule for a human or any other animal. The only dosage information provided is a range of 0.01-200 mg/kg. *Id.* at 9:1-12.

171. It is also my opinion that the specifications of the '330 patent fails to disclose a manner and process of “administering . . . an effective amount” in “full, clear, and concise, and exact terms” as to enable a person of ordinary skill in the art to practice the invention based solely on the

disclosed range of 0.01 mg/kg – 200 mg/kg, which constitutes a difference in magnitude of 20,000 times. As previously discussed, for average male with a weight of 70 kg, this dosing range translates to a dose between 7 mg to 14 g, which would require extensive studies to determine the appropriate amount to administer to the individual. Further, it is my understanding that it was known in the prior art that such generalized dosing guidelines can be highly inaccurate and that allometric calculations, when spread across various species can be highly variable, and lead to rapid toxicity. Boxembaum at 958 and 965; Collins at 791.

172. For at least these reasons, it is my opinion that claims 4, 10, 13, and 14 of the '330 patent are invalid under 35 U.S.C. § 112 for lack of enablement.

iv. The Specification of the '330 Patent Lacks Sufficient Written Description

173. It is my opinion that the specification of the '330 patent does not describe claims 4, 10, 13, and 14 in such a way that a person of ordinary skill in the art would understand that the inventors actually invented what is claimed.

174. Claims 4, 10, 13, and 14 of the '330 patent claims are directed to a method for treating a tumor of the liver or a method of treating liver cancer by administering an effective amount of sorafenib or a pharmaceutically acceptable salt thereof.

175. The '330 patent specification discloses a large class of compounds that inhibit the enzyme raf kinase yet the '330 patent does not disclose any specific data for any particular compound *See id.* at 9:48- 93:38. The '330 patent discloses 103 “exemplified compounds.” *Id.* at 43:9-92:45. Sorafenib is disclosed as “Entry 42.” The '330 patent discloses an in vitro raf kinase assay, in vitro cellular assays, and in vivo assay for testing the disclosed compounds. The only disclosed data is that, in the in vitro raf kinase assay, “[a]ll compounds exemplified displayed IC₅₀s

of between 1 nM and 10 μ M.” *Id.* at 92:48-49. ’330 patent at col.93, ll.48-49. The ’330 patent does not disclose any data at all for the in vitro cellular assays and in vivo assays, and the in vivo assays are described as assays that “can be performed.” *Id.* at 93:21-23.

176. Further, the specification does not mention the types of tumors or cancers recited in the claims – prostate, breast, liver, ovary, or cervix. Instead, the ’330 patent generally states that “the compounds of the invention are useful in treating cancers, including solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).” *Id.* at 1:65- 2:3.

177. Based on this understanding of the specification of the ’330 patent, it is my opinion that claims 4, 10, 13, and 14 lack sufficient written description.

v. The ’330 Patent Does Not Describe Methods of Treating Cancer

178. The general statement in the ’330 patent that “the compounds of the invention are useful in treating cancers, including solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma)” (*id.*), does not provide adequate written description for claims directed to the use of the disclosed compounds to treat cancer. ’330 patent at col.1 l.65-col.2 l.3. It is my opinion that non-specific data regarding an in vitro raf kinase assay, and general statements regarding predicted usefulness in treating cancer are insufficient to describe methods of actually using those compounds to treat cancer.

179. The ’330 patent’s disclosure of additional assays to assess the potency of the disclosed compounds, without providing any data, also provides no written description support for the claimed methods of using those compounds to treat cancer. Indeed, the ’330 patent provides

nothing more than a hypothesis that the 103 “exemplified compounds” might be useful for treating cancer because those compounds have some degree of raf kinase inhibition activity. The disclosure of assays that can be used to evaluate the potency of those compounds provides nothing more than a research plan to further investigate those compounds.

180. For at least these reasons, it is my opinion that the written description of the ’330 patent would not convey to one of ordinary skill in the art that the named inventors of the ’330 patent were in possession of methods of treating cancer, and as such claims 4, 10, 13, and 14 of the ’330 patent are invalid under 35 U.S.C. § 112 for lack of written description.

vi. The ’330 Patent Does Not Describe Treating the Types of Cancer Recited in the Claims

181. It is my opinion that even if the ’330 patent’s written description could be interpreted to describe some methods of treating cancer, the written description does not describe the ’330 patent’s claimed methods of treating a tumor or cancer of the liver, or any of the other organs claimed by the patent, including the prostate, breast, ovary, and cervix. In fact, none of those types of cancer are mentioned in the ’330 patent’s written description. The only possible disclosure in the ’330 patent that encompasses treating the types of cancer recited in the claims is the general statement that “the compounds of the invention are useful in treating cancers, including solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).” *Id.*

182. It is my opinion that because the ’330 patent does not sufficiently describe the treatment of any of the types of tumors or cancers recited in the asserted claims, claims 1, 4, 7, 10, and 13 of the ’330 patent are invalid under 35 U.S.C. § 112 for lack of written description

vii. The '330 Patent's Written Description Does Not Suggest The Claimed Methods

110. It is my opinion that because the written description of the '330 patent further indicates that the disclosed compounds would not be useful for treating any and all cancers, the written description of the '330 patent does not suggest the methods of claims 1, 4, 7, 10 and 13. The '330 patent states that the disclosed raf kinase inhibitors may be useful in treating cancer, "[s]ince the enzyme [raf kinase] is a downstream effector of p21ras." The specification also explains that the p21ras oncogene is mutated in only 30% of human cancers. *Id.* at 1:19-22, 55-60. It is my opinion that the '330 patents' written description, therefore, suggests that the disclosed compounds would not be useful in treating 70% of human cancers – namely, those not expressing the p21ras oncogene.

111. Further, it is my opinion that nothing in the '330 patent's written description even suggests that the disclosed compounds could treat any and all types of cancer generally, or those recited in the claims specifically.

112. It is also my opinion that the assays disclosed in the '330 patent do not relate to the cancers recited in the claims (prostate, liver, ovary, or cervix), with the exception of breast cancer. *See* '330 Notice Letter at 113 (citing to Monia, et al., "Antitumor activity of a phosphorothioate antisense oligodeoxynucleotide targeted against *C-raf* kinase," *Nature Med.*, 2:668-675 (1996)). Notably, Monia states that "little is known about the potential for development of resistant tumor cell populations that lose their sensitivity toward *C-raf* inhibition over time" and "some tumor cells may never display sensitivity towards *C-raf* inhibition" (Monia at 673), further supporting the conclusion that '330 patent's written description would not have demonstrated to a POSA that the named inventors had possession of methods of treating cancer.

113. For at least these reasons, it is my opinion that claims 1, 4, 7, 10, and 13 of the '330 patent are invalid under 35 U.S.C. § 112 for lack of written description.

1. Arguments During Prosecution Confirm the Inadequacy of the Written Description

114. It is my opinion that arguments made during the prosecution of the '330 patent confirm the inadequacy of the written description of claims 1, 4, 7, 10, and 13.

115. During prosecution of the '330 patent, the examiner found written description support for the claims based on the specification's recitation that "the compounds of the invention are useful in treating cancers, including solid cancers" (*id.* at 1:65-67), and based on several references provided by the applicant that purportedly recite the types of solid cancers recited in the claims. '330 File History, November 8, 2013 Office Action at 8-9. Also during prosecution, the applicant successfully argued that an obviousness-type double patenting rejection based on the '630 patent did not apply. *See* '330 Notice Letter at 47; '330 File History, February 10, 2014 Reply at 5 ("2/10/14 Reply").

116. Specifically, during prosecution of the '330 patent, the examiner issued an obviousness-type double patenting rejection of the pending claims over the parent '630 patent. To overcome this rejection, the applicant successfully argued that the claimed methods of treating cancer of the prostate, breast, liver, ovary, or cervix were not obvious in light of methods of treating the cancers recited in the claims of the '630 patent (lung, pancreas, thyroid, bladder, and colon). It is my opinion that the only carcinomas whose treatment is arguably disclosed in the written description of the '330 patent are those recited in the claims of the '630 patent.

117. Accordingly, it is my opinion that any argument that disclosure of methods of treating cancer of the lung, pancreas, thyroid, bladder, and colon described methods of treating cancer of

prostate, breast, liver, ovary, or cervix, would be clearly inconsistent with the argument during the prosecution that methods of treating the cancers recited in the '330 patent claims are "distinct cancers" that "are not obvious variants of" methods of treating the only carcinomas cited in the written description. 2/10/14 Reply at 5.

118. For at least these reasons, it is my opinion that claims 1, 4, 7, 10, and 13 of the '330 patent are invalid under 35 U.S.C. § 112 for lack of written description.

2. The '330 Patent Does Not Describe Treating Cancer By Administering Sorafenib

119. It is my opinion that the '330 patent does not provide any specific data regarding the efficacy of sorafenib (or any particular compound) in any in vitro or in vivo assays. As mentioned above, the only disclosed data is that, in the in vitro raf kinase assay, "[a]ll compounds exemplified displayed IC₅₀s of between 1 nM and 10 μM." '330 patent at 92:48-49. The '330 patent identifies 103 "exemplified compounds," but does not disclose the specific IC₅₀ value for any particular compound. Thus, the only information about the activity of sorafenib disclosed in the '330 patent is that sorafenib has IC₅₀ value somewhere between 1 nM and 10 μM in an in vitro raf kinase inhibition assay. This range of IC₅₀ values spans four orders of magnitude (10 μM = 10,000 nM).

120. It is my opinion that the '330 patent provides no description of the significance of those IC₅₀ value and provides no description linking those values to efficacy in treating cancer. Further, it is my opinion that the '330 patent provides no description to suggest that any compound having an IC₅₀ value less than 10,000 nM in an in vitro raf kinase could be used to treat cancer.

121. It is also my opinion that a person of ordinary skill in the art would not know from the '330 disclosure alone which of the 103 exemplified compounds are least or most potent, and would not know if any compound having an IC₅₀ value between these values in an in vitro raf kinase assay

could successfully treat cancer. It is my opinion that disclosing assays to evaluate the potency of the 103 exemplified compounds does not describe using any of those compounds to treat cancer. The limited data provided in the written description of the '330 patent would not have indicated to one of ordinary skill in the art that sorafenib in particular could be used to treat cancer.

122. For at least these reasons, it is my opinion that claims 1, 4, 7, 10, and 13 of the '330 patent are invalid under 35 U.S.C. § 112 for lack of written description.

Invalidity Of The '933 patent

123. The '933 patent issued from U.S Patent Application No. 11/664,363 which was the National Stage of Patent Cooperation Treaty Application No. PCT/EP2005/010119, filed on September 20, 2005. The PCT '119 application claimed priority to European Application No. EP 04 023 130, filed on September 29, 2004. For purposes of my analysis, I have assumed that the '933 patent is entitled to its earliest claimed priority date of September 29, 2004. My opinions would not change if it were entitled to priority only to September 20, 2005.

124. In forming my opinions, I have reviewed the '933 patent, the findings of Dr. Hollingsworth's Opening Expert Report, including his opinions and assessment of the asserted claims, and understand that it his opinion that sorafenib tosylate Polymorph I was either inherently the product of the prior art or obvious from the prior art, and was an obvious variant of the subject matter found in the prior art. I further understand from Dr. Hollingsworth that Polymorph I is described in the patent as the most stable sorafenib tosylate polymorph at room temperature. '933 patent at 2:30-37.

i. Claims 8-10 Are Invalid For Anticipation And Or Obvious

125. Claims 8, 9, 10 of '933 patent relate to pharmaceutical formulations comprising sorafenib tosylate Polymorph I. I understand from Dr. Hollingsworth's opening expert report that it

was common to select the most stable polymorph of an active pharmaceutical ingredient for use in a pharmaceutical composition because it would change form over the course of storage. *See* Hollingsworth Op. Ex. Rep.

126. An active ingredient like sorafenib tosylate must be given to a patient in dosage form (e.g. tablet) which is a pharmaceutical composition. WO 228 discloses the use of sorafenib tosylate in pharmaceutical compositions such as “orally, topically, parenterally, by inhalation or spray or vaginally, sublingually, or rectally in dosage unit formulations.” WO 228 at 25. As a result, Claim 8 is anticipated by WO 228, or obvious over the prior art including WO 228 and Carter.

127. Claim 9 depends from claim 8 and includes the further limitation of including inert, nontoxic, pharmaceutically suitable excipients in the composition. An active ingredient like sorafenib tosylate must be given to a patient in dosage form (e.g. tablet) that necessarily includes inert, nontoxic, pharmaceutically suitable excipients. Numerous prior art references, including WO 228 disclose the use of such excipients. Similarly, Carter discloses the use of such excipients together with raf kinase inhibitors. As a result, Claim 8 is anticipated by WO 228, or obvious over the prior art including WO 228 and Carter.

128. Claim 10 depends from claim 8 and specifies that the sorafenib tosylate present in the composition be at least 90% (by weight) sorafenib tosylate Polymorph I. I understand from Dr. Hollingsworth that it is most common to use material that was purely one polymorph—particularly the most stable polymorph—in a pharmaceutical composition to avoid the risk of conversion from one polymorph to another. *See* Hollingsworth Op. Ex. Rep.

129. Accordingly, claims 8-10 are invalid as anticipated and/or obvious.

ii. Claims 16, 18, 19 And 21 Of The '933 Patent Are Invalid for Anticipation And/Or Obvious

130. Claim 16 relates to administering a therapeutically effective amount of sorafenib tosylate Polymorph I. Because sorafenib tosylate was a known active pharmaceutical composition, it would have been obvious to administer an effective amount to treat some condition. More specifically, WO 228 specifically discloses “A method of treating disease mediated by VEGF-induced signal transduction pathway comprising administering [sorafenib tosylate].” *Id.* at 74. As a result, Claim 16 is anticipated by WO 228, or obvious in view of the prior art.

131. Claim 17 depends from claim 16 and specifies that the disorder is abnormal angiogenesis, hyperpermeability processes, bone marrow diseases, carcinoma and carcinogenic cell growth. WO 228 discloses that the compounds of the publication “will be useful in treatment of diseases characterized by abnormal angiogenesis and/or hyperpermeability processes.” *Id.* at 3, 17. Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. *Id.* at [0036], [0045]. Combined with the reasons articulated above for claim 16, claim 17 is invalid as anticipated over WO 228 or obvious in view of the prior art.

132. Claim 18 depends from claim 16 and specifies that the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid, kidney, or intestine. WO 228 discloses that the compounds of the publication “will be useful in treatment of diseases characterized by abnormal angiogenesis and/or hyperpermeability processes.” *Id.* at 3, 17. Among the diseases disclosed is “tumor growth.” Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. *Id.* at

[0036], [0045]. Combined with the reasons articulated above for claim 17, claim 18 is invalid as anticipated over WO 228 or obvious in view of the prior art.

133. Claim 19 recites a method for treating a disorder, comprising administering a therapeutically effective amount of the compositions of any one of claims 8 to 15. For the same reasons articulated for claims 8 to 10 and claims 16-18, claim 19 is invalid as anticipated and/or obvious.

134. Claim 20 depends from claim 19 and specifies that the disorder is abnormal angiogenesis, hyperpermiability processes, bone marrow diseases, carcinoma and carcinogenic cell growth. WO 228 discloses that the compounds of the publication “will be useful in treatment of diseases characterized by abnormal angiogenesis and/or hyperpermeability processes.” *Id.* at 3, 17. Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas.

135. Combined with the reasons articulated above for claim 16, 17, 18 and 19, claim 20 is invalid as anticipated by WO 228 and/or obvious over the prior art.

136. Claim 21 depends from claim 19 and specifies that the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid, kidney, or intestine. Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. *Id.* at [0036], [0045]. Combined with the reasons articulated above for claim 1, 17 and 19, and 20, Claim 21 is invalid as obvious.

iii. Claims 10, 16, 18-19, 21, 41 are Invalid for Double Patenting Over Claim 41 of the '834 patent

137. As described above, Claim 41 of the '834 patent is directed to: "A compound of claim 39 which is [sorafenib tosylate]." '834 patent at 100:46-48. For the same reasons described above regarding anticipation and obviousness, each of claims 10, 16, 18-19, 21, and 41 of the '933 patent are obvious variants of Claim 41 of the '834, i.e. sorafenib tosylate.

iv. Claims 10, 16, 18-19 and 21 are Obvious Variants of Claims 7-9 of the '141 patent

138. Claim 6-12 of the '141 patent generally relate to the use of sorafenib tosylate in methods of blocking tumor angiogenesis in a human or other mammal where the tumor of the breast, gastrointestinal tract, kidney, ovary or cervix. For the same reasons described above regarding anticipation and obviousness, each of claims 10, 16, 18-19 and 21 are obvious variants of these methods of using sorafenib tosylate, if not anticipated.

V. SUPPLEMENTAL OPINIONS

139. In the event that Plaintiffs should submit any response to my report, I reserve the right to respond to any issues raised by that response, including expert reports.

140. I specifically reserve my right to provide additional opinions regarding secondary considerations of nonobviousness. I understand that under the Scheduling Order in this case, Defendants need not address evidence of secondary considerations in their opening round of expert reports; rather, secondary considerations shall be addressed by Plaintiffs in the second round of expert reports, and Defendants shall respond to such evidence in the reply round of expert reports.

141. If called to testify, my testimony may include an explanation of scientific principles that underlie the opinions expressed in this report.

142. I have based my opinions and analyses on documents and information available to me at the time I signed the report. If and when any new evidence arises, I reserve the right to supplement or modify my opinions to reflect that evidence.

143. I reserve the right to prepare demonstratives to help explain my opinions.

A handwritten signature in black ink, reading "Michael Grossbard MD". The signature is written in a cursive style with a horizontal line underneath it.

MICHAEL GROSSBARD, M.D.

APRIL 13, 2017

EXHIBIT 7

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

BAYER HEALTHCARE LLC, BAYER)
 HEALTHCARE PHARMACEUTICALS INC.,)
 and ONYX PHARMACEUTICALS, INC.,)
)
 Plaintiffs,) C.A. No. 15-114-LPS
) (cons.)
 v.)
) **CONFIDENTIAL**
)
 MYLAN PHARMACEUTICALS INC.,)
)
 Defendant.)

**DEFENDANT’S THIRD SUPPLEMENTAL OBJECTIONS AND RESPONSES
TO PLAINTIFFS BAYER HEALTHCARE LLC, BAYER HEALTHCARE
PHARMACEUTICALS INC. AND ONYX PHARMACEUTICALS, INC.’S
FIRST SET OF INTERROGATORIES**

Pursuant to Rules 26 and 33 of the Federal Rules of Civil Procedure, Defendant Mylan Pharmaceuticals Inc. (“Mylan”) hereby objects and responds to Plaintiffs Bayer Healthcare LLC, Bayer Healthcare Pharmaceuticals Inc., and Onyx Pharmaceuticals Inc.’s (collectively, “Plaintiffs”) First Set of Interrogatories. These objections and responses are based on Mylan’s current understanding, knowledge and belief. As discovery has just commenced and the case is in its early stage, Mylan’s factual investigation and trial preparation is ongoing. Mylan reserves the right to supplement its responses as discovery progresses in this action.

GENERAL OBJECTIONS

Mylan makes the following General Objections to each Interrogatory:

1. Mylan incorporates by reference all objections set forth in the General Objections of Mylan's Responses to Plaintiffs' First Set of Requests for Production (Nos. 1-49).

2. Mylan objects to each Interrogatory to the extent it seeks information protected from disclosure by the attorney-client privilege, the work product doctrine, the common interest doctrine, or any other applicable privilege or immunity. Such information shall not be provided in response to any Interrogatory and any inadvertent disclosure thereof shall not be deemed a waiver of any privilege with respect to such information, or of any work product protection, which may attach thereto.

3. In furnishing these objections and responses to these interrogatories, Mylan does not admit or concede the relevance, materiality, authenticity, or admissibility in evidence of any such interrogatory or response, or to any documents or information produced in response to a particular interrogatory. All objections to the use, at trial or otherwise, of any information or documents provided in response to these interrogatories are hereby expressly reserved.

4. Mylan objects to each interrogatory, definition, or instruction as overly broad, unduly burdensome, oppressive, and seeking information not relevant to any party's claim or defense nor proportional to the needs of the case (in accordance with Fed. R. Civ. P. 26(b)(1)) to the extent that it seeks or purports to seek information relating to information other than the subject matter of ANDA No. 207012 and will not produce such information.

5. Mylan objects to each interrogatory, definition, or instruction to the extent that it prematurely seeks production of information to be provided during expert discovery. Mylan will not prematurely respond with information that is to be provided during expert discovery, but will only respond in accordance with the Court's schedule for expert discovery. Mylan is available to meet and confer with Plaintiffs to determine an appropriate discovery schedule for the provision of information, documents, and things in accordance with the Scheduling Order, Local Rules for the District of Delaware, the Default Standard for Discovery Including Discovery of ESI, and the Federal Rules of Civil Procedure.

6. Mylan objects to each interrogatory to the extent that it seeks information, documents, or things containing private, confidential, secret, trade secret, proprietary, and/or sensitive business information of Mylan, its employees, and/or third parties ("Confidential

Information”). Mylan will not produce Confidential Information to the extent that Mylan is under any obligation—whether imposed by a third party, court, tribunal, legislature, or any other body with authority to impose or enforce such an agreement, or by any statute, regulation, or order—to maintain it in confidence and not disclose it, and all of Mylan responses should be read to exclude the production of such information. In addition, Mylan will not produce Confidential Information, and will redact Confidential Information from documents and information that it produces, to the extent that such Confidential Information is not relevant to any claim or defense in this action nor reasonably calculated to lead to the discovery of admissible evidence. The Confidential Information that Mylan will withhold and/or redact includes, but is not limited to, Confidential Information pertaining to individual patients involved in clinical trials; clinical trial investigators’ personal information; the personal information of Mylan’s employees; the configuration of Mylan’s information technology systems; Mylan drugs not investigated or developed as part of the development of sorafenib; drugs belonging to other companies that have not received FDA approval; sales and budget forecasts; materials concerning the negotiation of agreements with third parties. All of Mylan’s responses should be read to exclude the production of such information. Mylan will only produce other Confidential Information pursuant to the Protective Order in this action.

7. Mylan’s responses herein are based on facts presently known to Mylan and represent a diligent and good faith effort to respond to the interrogatories. Mylan’s discovery and investigation into the matters specified is continuing. Accordingly, Mylan reserves the right to supplement, alter or change its responses and objections to these interrogatories and to produce additional responsive information or documents, if any, that Mylan has in its possession, custody, or control at the time the interrogatories were propounded. Furthermore, Mylan reserves the right, at trial or during other proceedings in this action, to rely on documents, evidence, and other matters in addition to the documents or information produced in response to the interrogatories, whether or not such documents, evidence, or other matters

are newly discovered or are now in existence but have not been identified or produced despite diligent and good faith efforts.

8. Mylan objects to each interrogatory, definition, or instruction to the extent that it seeks production of documents and electronically stored information from countries other than the United States relating to ANDA No. 207012, on the grounds that such interrogatories are overly broad, unduly burdensome, and seek information not relevant to any party's claim or defense nor proportional to the needs of the case (in accordance with Fed. R. Civ. P. 26(b)(1)). Mylan will not produce such information, and Mylan's responses should be read to exclude the production of such documents and electronically stored information.

9. Mylan objects to each interrogatory, definition, or instruction to the extent it calls for the production of draft articles, submissions, publications or other documents, on the ground and to the extent that production of drafts of documents is unduly burdensome and not relevant to any party's claim or defense nor proportional to the needs of the case (in accordance with Fed. R. Civ. P. 26(b)(1)).

10. Mylan objects to each Interrogatory on the ground it seeks information concerning, and the disclosure of, proprietary and highly confidential information. If and to the extent Mylan agrees to provide any information, it will do so only subject to the protections of the protective order and/or a mutually acceptable supplemental protective order to address Mylan's confidentiality concerns.

11. Mylan objects to each Interrogatory to the extent it seeks information that is already in Plaintiffs' possession, custody, or control, or that are as readily available to Plaintiffs as they are to Mylan.

12. Mylan objects to each Interrogatory to the extent it seeks information whose disclosure is governed by Mylan's agreements with third parties, including confidentiality agreements. Mylan will provide such information only after complying with, and in compliance with, the terms of such third-party agreements.

13. Mylan objects to each Interrogatory to the extent it seeks information disclosure of which is governed by a protective order entered by a Court. Mylan will provide such information only after complying with, and in compliance with, the terms of the protective order.

14. Mylan objects to each Interrogatory, alone or in conjunction with the Definitions and Instructions that purports to impose obligations not imposed or contemplated by the Federal Rules of Civil Procedure, the Local Rules of the District of Delaware, or any agreements or stipulations entered into by the parties.

15. Mylan objects to each Interrogatory to the extent it assumes a disputed fact or legal conclusion in defining the information requested. Mylan denies any such disputed facts or legal conclusions assumed by such Interrogatory, and any response or objection to any Interrogatory is without prejudice to this objection.

16. Mylan objects to each Interrogatory to the extent it seeks information dated or prepared on or after January 30, 2015, the date of commencement of this litigation.

17. Mylan objects to each interrogatory to the extent it is directed at multiple issues and/or multiple parties, and thus constitutes multiple interrogatories under the guise of a single interrogatory. By responding to the interrogatories, Mylan in no way waives its right to object to the number of interrogatories, including subparts, which Plaintiffs have propounded or will propound in this action.

OBJECTIONS TO DEFINITIONS AND INSTRUCTIONS

18. Mylan objects to the definition of “Mylan’s ANDA Product” to the extent such term is overbroad and includes information that is not related to any claim or defense in this action, and is not reasonably calculated to lead to the discovery or admissible evidence and/or includes information outside of Mylan’s possession, custody, or control.

19. Mylan objects to the definition of “document” to the extent such term is overbroad and imposes discovery obligations broader than those imposed by the Federal Rules of Civil Procedure, the Local Rules for the District of Delaware, any Court orders, or any

agreements or stipulations entered into by the parties. Mylan will comply with Plaintiffs' Interrogatories pursuant to its obligations under Federal Rules of Civil Procedure, the Local Rules for the District of Delaware, the Court's Scheduling Order entered in this case (Dkt. 33), or any agreements or stipulations entered into by the parties.

20. Mylan objects to Plaintiffs' definition of "you," "your," "yours," and "Mylan" as overly broad to the extent that it refers to the officers, directors, employees, divisions, parent companies, subsidiaries, affiliates, predecessors, or successors-in-interest, and any joint venture associated with Defendants, etc. Documents and electronically stored information in the possession, custody, or control of Mylan's officers, directors, employees, divisions, parent companies, subsidiaries, affiliates, predecessors, or successors-in-interest, and any joint venture associated with Defendants, etc., are not necessarily in the possession, custody, or control of Mylan, and Mylan will not construe the interrogatories to require production of such documents or electronically stored information to the extent that they are not in the possession, custody, or control of Mylan. Mylan responds on behalf of Mylan alone.

21. Mylan objects to each interrogatory, definition, and instruction to the extent that it seeks identification of "any" or "all" documents, information, communications, locations, persons, or corporations or other entities responsive to the interrogatory. Such demands are unduly burdensome and overly broad, and they seek documents and information that are not relevant to the claim or defense of any party nor proportional to the needs of the case, considering the importance of the issues at stake in the action, the amount in controversy, the parties' relative access to relevant information, the parties' resources, the importance of the discovery in resolving the issues, and whether the burden or expense of the proposed discovery outweighs its likely benefit. Indeed, many of Bayer's interrogatories are exceedingly broad—and constitute multiple interrogatories written in the form of a single interrogatory—and it would be extremely burdensome to respond to them. Mylan will use reasonable diligence to respond to Bayer's interrogatories based on information and/or documents in its possession, custody, or control, including based on a reasonable search of those files that are reasonably

accessible and in which such information or documents ordinarily would be found and of files of those individuals whom Mylan reasonably believes are most likely to have responsive documents and/or information about the specific matters at issue. Where Mylan indicates that it will produce documents in response to an interrogatory, it means that it will produce only those non-privileged responsive documents that it was able to identify and locate after such a reasonable search, if any, as set forth above. Mylan construes the interrogatories only to require the production of such responsive documents or information.

22. Mylan objects to the definition of “identify” insofar as this term requests that Mylan in that it requires Mylan, with respect to documents, to identify the “type of document,” “general subject matter,” “date of the document,” “author(s),” “addressee(s),” and “recipient(s).” The burden is the same for Bayer to discern this information upon review of the documents as it would be for Mylan. Mylan objects insofar as the definition imposes discovery obligations broader than those imposed by the Federal Rules of Civil Procedure, the Local Rules for the District of Delaware, any Court orders, or any agreements or stipulations entered into by the parties. Mylan will comply with Plaintiffs’ Interrogatories pursuant to its obligations under Federal Rules of Civil Procedure, the Local Rules for the District of Delaware, the Court’s Scheduling Order entered in this case (Dkt. 33), or any agreements or stipulations entered into by the parties.

23. Mylan objects to Instruction No. 7 insofar as it imposes discovery obligations broader than those imposed by the Federal Rules of Civil Procedure, the Local Rules for the District of Delaware, any Court orders, or any agreements or stipulations entered into by the parties. Mylan will provide a privilege log pursuant to the parties’ Stipulation and Order on E-Discovery, or any other agreements or stipulations entered into by the parties.

SPECIFIC OBJECTIONS AND RESPONSES

INTERROGATORY NO. 1:

Do you contend that the manufacture, use, sale, offer for sale, or importation of Mylan’s ANDA Product, including use of Mylan’s ANDA Product in accordance with the proposed

labeling (including the prescribing information and patient package insert) for such product, would not infringe one or more claims of the patents-in-suit, assuming the claims to be valid and enforceable? If your answer is that one or more of these claims would not be infringed, identify the claims that you contend would not be infringed, state all bases on which you contend any such claim would not be infringed either literally or under the doctrine of equivalents, including any basis upon which you assert that Plaintiffs are estopped from asserting infringement by the doctrine of equivalents, state all facts on which you rely for your contentions, and identify all documents and circumstances relating to those facts and all individuals with knowledge of those facts.

RESPONSE TO INTERROGATORY NO. 1:

Mylan incorporates the General Objections set forth above. Mylan objects to this interrogatory as overly broad, unduly burdensome, and oppressive to the extent it seeks information that is irrelevant to the claims and defenses at issue in this case and is not proportional to the needs of the case. For example, Mylan objects to the phrase “all bases,” “any basis,” “all facts,” “all documents and circumstances,” and “all individuals” as being overly broad and requiring the production of trivial documents and other documents with limited, if any, relevance to the parties’ claims or defenses. Mylan further objects to the phrases “one or more claims” and “any such claim” to the extent that this interrogatory seeks information not relevant to the Asserted Claims. Mylan will be responding to this interrogatory only insofar as it is relevant to the claims currently asserted by Plaintiffs. Mylan objects to this Interrogatory to the extent it calls for a legal conclusion. Mylan further objects to this interrogatory as premature under the Scheduling Order, as discovery is just beginning, Mylan has not received any discovery from Bayer, and no depositions have been conducted. Mylan further objects to this interrogatory to the extent that Mylan does not bear the burden of proof regarding infringement. Mylan further objects to this interrogatory as premature under the Local Rules and the Default Standard for Discovery Including Discovery of ESI, which requires Plaintiffs to produce initial claim charts demonstrating how each product allegedly

infringes each asserted patent claim before Defendants provide any initial contentions. This interrogatory essentially requires Mylan to provide non-infringement contentions before Plaintiffs have provided its infringement contentions. Mylan further objects to this interrogatory as seeking expert discovery prior to the dates for expert reports. Mylan objects to this interrogatory to the extent it seeks information that is confidential, protected by the right of privacy, and/or protected from disclosure by applicable privileges and protections, including without limitation the attorney-client privilege, work product protection, common interest privilege and/or consulting expert privilege. Mylan objects to this interrogatory to the extent it seeks information the disclosure of which is subject to third-party confidentiality obligations or a protective order. Mylan objects to this interrogatory to the extent it requests information not in Mylan's possession, custody, or control. Mylan objects to this interrogatory to the extent it calls for information already in Plaintiffs' possession, or calls for publicly available information. Mylan objects to this interrogatory as vague and ambiguous as to the terms "proposed labeling" and "circumstances." Mylan proposes that the parties meet and confer to determine a meaning. Mylan objects to this interrogatory to the extent it includes multiple subparts, each of which constitutes a separate Interrogatory pursuant to Fed. R. Civ. P. 33(a)(1). Mylan further objects to this interrogatory as improper under Fed. R. Civ. P. 33(a) because it purports to be a single interrogatory but contains multiple subparts. This interrogatory has at least five discrete subparts and is, therefore, at least five interrogatories. Mylan further objects to the description of this interrogatory as Interrogatory No. 1. Mylan considers this interrogatory to be Interrogatory Nos. 1-5.

Subject to and without waiving the foregoing objections, and to the extent understood, Mylan responds that it is Plaintiffs' burden to provide initial infringement contentions under the Scheduling Order. Mylan will supplement its response after Plaintiffs provide appropriate infringement contentions.

Discovery is on-going and Mylan will supplement its response if necessary and in accordance with the Federal Rules of Civil Procedure. Mylan is available to meet and confer

with Plaintiffs to determine an appropriate discovery schedule for the provision of information, documents, and things in accordance with the Scheduling Order, Local Rules for the District of Delaware, the Default Standard for Discovery Including Discovery of ESI, and the Federal Rules of Civil Procedure.

FIRST SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 1

Mylan incorporates by reference the General Objections, Objections to Definitions and Instructions, and each specific objection set forth above as if fully stated herein. Mylan further objects to this interrogatory as premature and improper because it assumes that the Asserted Claims are valid and enforceable, which Mylan contends. Mylan supplements its response to Interrogatory No. 1 as follows:

[REDACTED]

These amended contentions are based on information reasonably available to Mylan at this time. These contentions are necessarily preliminary and may require subsequent amendment, alteration or supplementation. By submitting these contentions, Mylan does not waive its claims or defenses in this case.

These contentions do not indicate Mylan's position with regard to the proper claim construction of any term of the Asserted Claims. Mylan has made reasonable assumptions, to the extent necessary and appropriate, with respect to the meaning of patent claim terms for the purpose of preparing these contentions.

Mylan reserves the right to rely upon different meanings in the conduct of this litigation and to assert different meanings as appropriate in connection with Markman procedures and proceedings. Mylan further reserves the right to update these contentions following a Markman

opinion adopting meanings that differ from those assumed by Mylan or any other judicial clarification or alteration of the meaning of claim terms, and/or as otherwise authorized or permitted by the Local Rules of the District of Delaware and the Federal Rules of Civil Procedure.

In addition, Mylan reserves its right to amend, alter, or supplement these contentions at any time and/or as otherwise authorized or permitted by the aforesaid Rules, based upon further investigation, materials arising from fact or expert discovery, elucidation of Plaintiffs' infringement positions, claim construction from the Court, any alteration to the claims asserted, positions on claim construction or infringement taken by Plaintiffs, or as otherwise necessary and appropriate under the Local Patent Rules or any other applicable Rules or order of the Court. Mylan reserves the right to supplement these contentions to incorporate arguments set forth in disclosures by any other parties in this action or any other action involving the Asserted Patents or related patents. These contentions may be asserted in the alternative and do not constitute any concession by Mylan for purposes of claim construction or infringement. See Fed. R. Civ. P. 8(d).

Furthermore, these contentions are provided without prejudice to the rights of Mylan to introduce at trial any subsequently-discovered evidence or expert opinions relating to currently-known facts and to produce and introduce at trial all evidence, whenever discovered, relating to the proof of subsequently-discovered facts. Moreover, facts, documents and things now known may be imperfectly understood and, accordingly, such facts, documents and things may not have been included in this statement. Mylan reserves its right to refer to, conduct discovery with reference to, or offer into evidence at the time of trial, any and all facts, expert opinion testimony, documents and things notwithstanding the written statements herein and subject to the Rules of this Court. Mylan further reserves its right to refer to, conduct discovery with reference to, or offer into evidence at the time of trial, any and all facts, documents and things that are not currently recalled but might be recalled at some time in the future.

Mylan objects to the disclosure of information that is protected by the attorney-client privilege, attorney work-product immunity, the common interest privilege, or any other applicable privilege or immunity. To the extent that Mylan inadvertently discloses information that may be protected from discovery under the attorney-client privilege, the attorney work-product immunity, the common interest privilege or any other applicable privilege or immunity, such inadvertent disclosure does not constitute a waiver of any such privilege or immunity.

The information set forth below is provided without waiver of (1) the right to object to the use of any statement for any purpose, in this action or in any other action, on the grounds of privilege, relevance, materiality or any other appropriate grounds; (2) the right to object to any request involving or relating to the subject matter of the statements herein; or (3) the right to revise, correct, supplement or clarify any of the statements provided below at any time.

[REDACTED]
 [REDACTED]
 [REDACTED]
 [REDACTED]

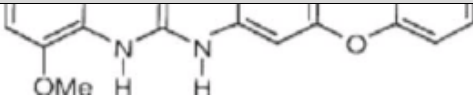
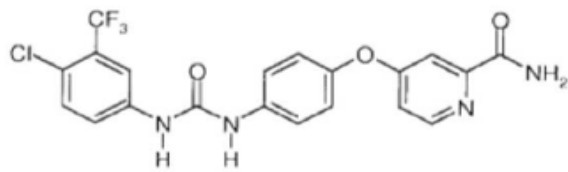
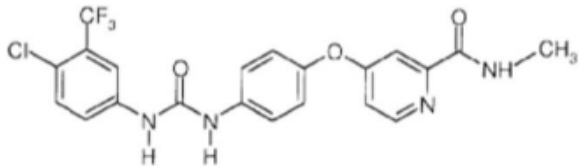
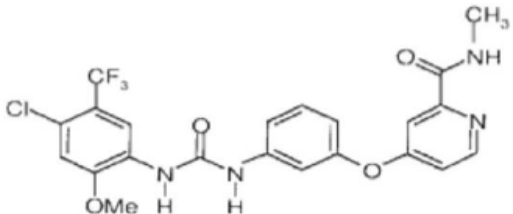
[illegible]

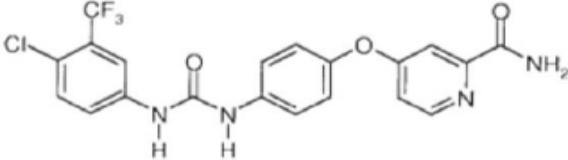
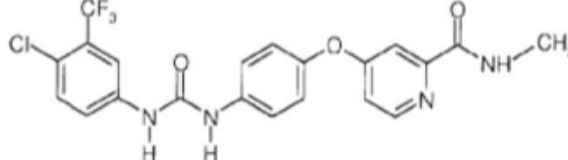
Subject to the foregoing, Mylan's ANDA Products do not infringe the Asserted Claims for at least the following reasons:

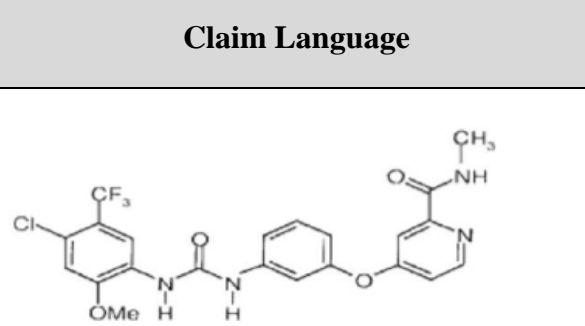
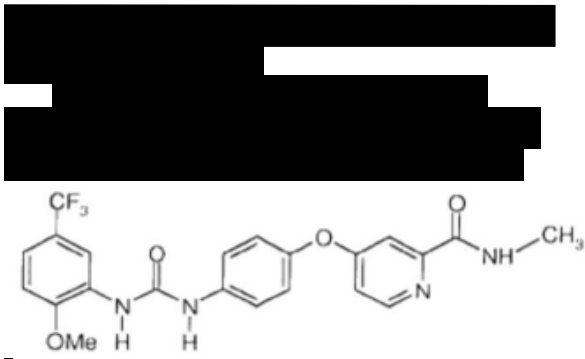
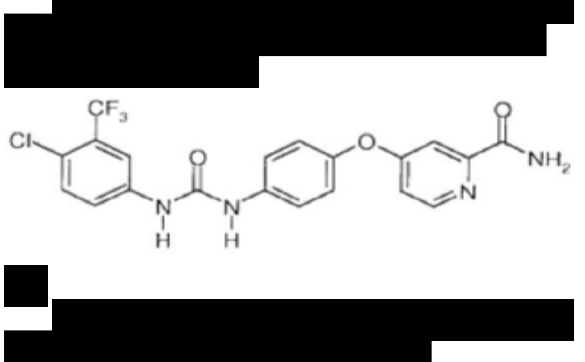
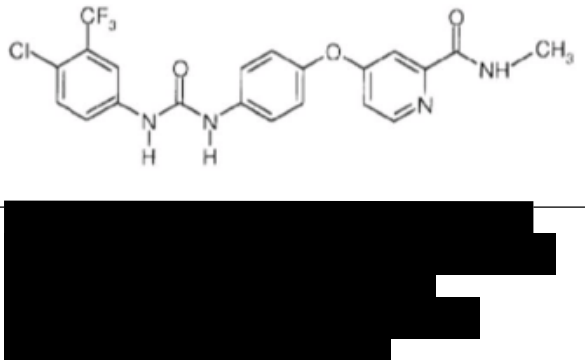
Claim Language	Mylan's ANDA Product
[REDACTED]	[REDACTED]
[REDACTED]	[REDACTED]

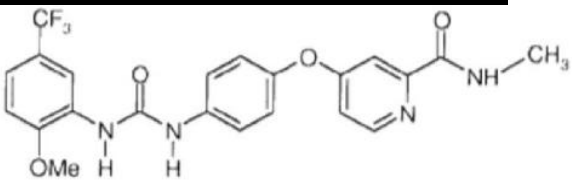
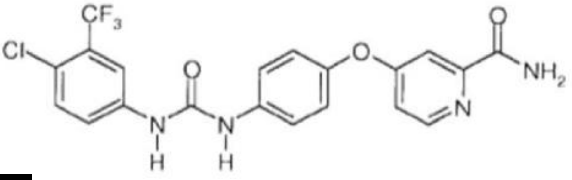
Claim Language	Mylan's ANDA Product
<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>

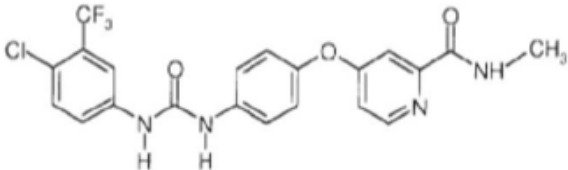
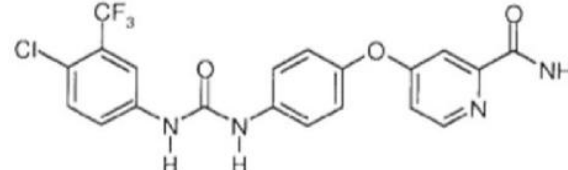
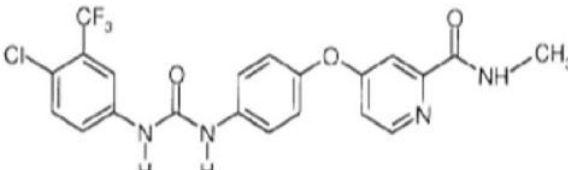
Claim Language	Mylan's ANDA Product
<p>[REDACTED]</p> <p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
<p></p> <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p>




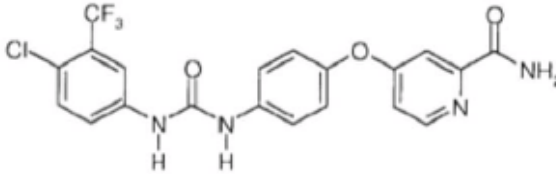


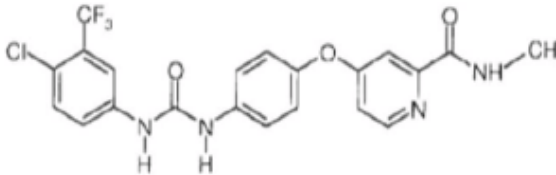
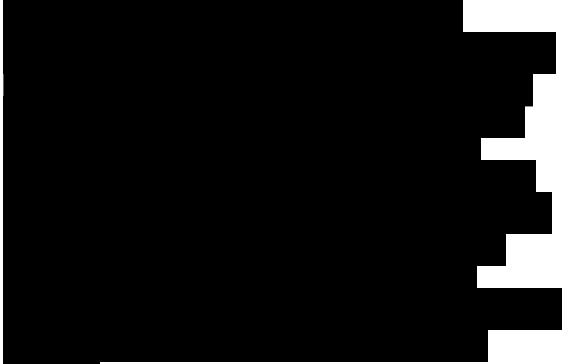



Claim Language	Mylan's ANDA Product
	
	
	
	

Claim Language	Mylan's ANDA Product
<p>[REDACTED]</p>	<p>[REDACTED]</p>
<p>[REDACTED]</p> <p></p> <p>[REDACTED]</p> <p></p> <p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p>

Claim Language	Mylan's ANDA Product
	
	
	
	

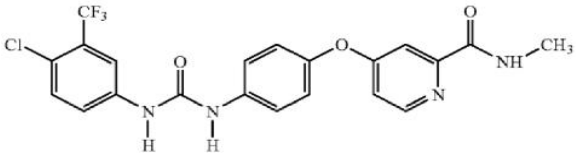
Claim Language	Mylan's ANDA Product
<p>[REDACTED]</p>	<p>[REDACTED]</p>
<p>[REDACTED]</p> <p>[REDACTED]</p> <p></p> <p>[REDACTED]</p> <p>[REDACTED]</p> <p></p> <p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p>

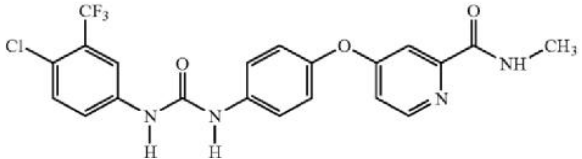
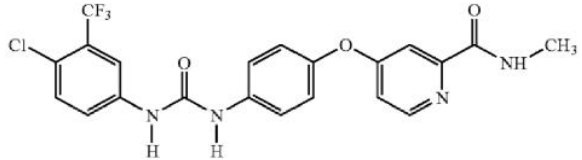
Claim Language	Mylan's ANDA Product
	
 	

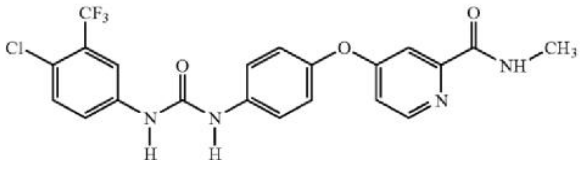
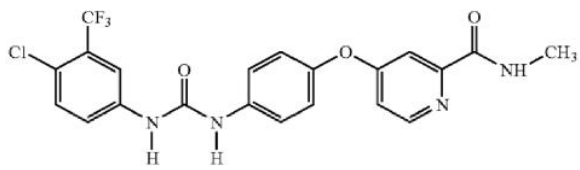
Claim Language	Mylan's ANDA Product
	
<p data-bbox="204 684 699 758"></p> <p data-bbox="204 783 773 898"></p> <p data-bbox="204 968 773 1140"></p> <p data-bbox="204 1209 228 1251"></p> <p data-bbox="204 1276 764 1392"></p> <p data-bbox="204 1444 773 1617"></p>	 
	

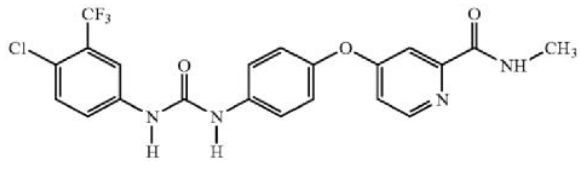
Claim Language	Mylan's ANDA Product
<p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p>

II. THE '623 PATENT

Claim Language	Mylan's ANDA Product
<p>[REDACTED]</p> <p>(X)</p>  <p>[REDACTED]</p> <p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p>

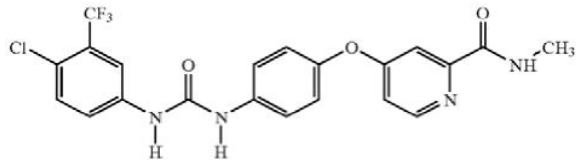
Claim Language	Mylan's ANDA Product
<div data-bbox="203 317 781 548" data-label="Text"><p>[REDACTED]</p></div> <div data-bbox="203 569 781 768" data-label="Chemical-Block"><p>(X)</p><p>The chemical structure shows a 2-chloro-4-(trifluoromethyl)phenyl ring connected to a pyridine ring via a hydrazide linker. The pyridine ring has a methoxy group at the 4-position and a methylcarbamoyl group at the 2-position.</p></div> <div data-bbox="812 291 1421 1136" data-label="Text"><p>[REDACTED]</p></div>	<div data-bbox="821 317 1399 506" data-label="Text"><p>[REDACTED]</p></div> <div data-bbox="821 527 1399 894" data-label="Text"><p>[REDACTED]</p></div> <div data-bbox="821 894 1399 1125" data-label="Text"><p>[REDACTED]</p></div>
<div data-bbox="203 1163 781 1320" data-label="Text"><p>[REDACTED]</p></div> <div data-bbox="203 1341 781 1541" data-label="Chemical-Block"><p>(X)</p><p>The chemical structure is identical to the one in the first row, showing a 2-chloro-4-(trifluoromethyl)phenyl ring connected to a pyridine ring via a hydrazide linker. The pyridine ring has a methoxy group at the 4-position and a methylcarbamoyl group at the 2-position.</p></div> <div data-bbox="203 1562 781 1614" data-label="Text"><p>[REDACTED]</p></div> <div data-bbox="203 1698 781 1751" data-label="Text"><p>[REDACTED]</p></div> <div data-bbox="812 1138 1421 1772" data-label="Text"><p>[REDACTED]</p></div>	<div data-bbox="821 1142 1399 1509" data-label="Text"><p>[REDACTED]</p></div> <div data-bbox="821 1509 1399 1751" data-label="Text"><p>[REDACTED]</p></div>
<div data-bbox="203 1799 781 1875" data-label="Text"><p>[REDACTED]</p></div>	<div data-bbox="821 1799 1399 1875" data-label="Text"><p>[REDACTED]</p></div>

Claim Language	Mylan's ANDA Product
<p data-bbox="203 294 779 441">[REDACTED]</p> <div data-bbox="203 462 779 672"><p data-bbox="747 462 779 493">(X)</p><chem>CCNC(=O)c1cc(Oc2ccc(cc2)N(C(=O)Nc3cc(C(F)(F)F)cc3Cl)cn1)ccn1</chem></div>	<p data-bbox="820 294 1421 399">[REDACTED]</p> <p data-bbox="820 420 1421 787">[REDACTED]</p> <p data-bbox="820 798 1421 1018">[REDACTED]</p>
<p data-bbox="203 1050 779 1207">[REDACTED]</p> <div data-bbox="203 1228 779 1438"><p data-bbox="747 1228 779 1260">(X)</p><chem>CCNC(=O)c1cc(Oc2ccc(cc2)N(C(=O)Nc3cc(C(F)(F)F)cc3Cl)cn1)ccn1</chem></div> <p data-bbox="203 1459 779 1501">[REDACTED]</p> <p data-bbox="203 1585 779 1669">[REDACTED]</p>	<p data-bbox="820 1050 1421 1396">[REDACTED]</p> <p data-bbox="820 1407 1421 1638">[REDACTED]</p>
<p data-bbox="203 1722 779 1869">[REDACTED]</p>	<p data-bbox="820 1722 1421 1848">[REDACTED]</p>

Claim Language	Mylan's ANDA Product
<p data-bbox="203 294 779 367">[REDACTED]</p> <div data-bbox="203 388 779 598"><p data-bbox="747 388 779 430">(X)</p><chem>CC(=O)Nc1cc(Oc2ccc(cc2)Nc3cc(C(F)(F)F)c(Cl)c3)ccn1</chem></div>	<p data-bbox="820 294 1356 367">[REDACTED]</p> <p data-bbox="820 388 1388 808">[REDACTED]</p> <p data-bbox="820 819 1388 1039">[REDACTED]</p>
<p data-bbox="203 1071 771 1228">[REDACTED]</p>	<p data-bbox="820 1071 1388 1270">[REDACTED]</p> <p data-bbox="820 1281 1388 1648">[REDACTED]</p> <p data-bbox="820 1659 1388 1879">[REDACTED]</p>

Claim Language	Mylan's ANDA Product
<div data-bbox="203 321 771 472" style="background-color: black; width: 100%; height: 50px;"></div>	<div data-bbox="824 321 1388 508" style="background-color: black; width: 100%; height: 50px;"></div> <div data-bbox="824 535 1388 892" style="background-color: black; width: 100%; height: 100px;"></div> <div data-bbox="824 903 1388 1123" style="background-color: black; width: 100%; height: 80px;"></div>

III. THE '834 PATENT

Claim Language	Mylan's ANDA Product
<div data-bbox="203 1367 779 1522" style="background-color: black; width: 100%; height: 50px;"></div> <div data-bbox="203 1549 779 1743" style="text-align: center;"> <p>(X)</p>  <chem>CC(=O)Nc1ccc(Oc2ccc(NC(=O)Nc3ccc(Cl)c(C(F)(F)F)c3)cc2)cn1</chem> </div> <div data-bbox="203 1770 779 1816" style="background-color: black; width: 100%; height: 20px;"></div>	<div data-bbox="824 1350 1388 1732" style="background-color: black; width: 100%; height: 100px;"></div> <div data-bbox="824 1743 1388 1869" style="background-color: black; width: 100%; height: 40px;"></div>

Claim Language	Mylan's ANDA Product
<p>[REDACTED]</p>	<p>[REDACTED]</p>
<p>[REDACTED]</p>	<p>[REDACTED]</p>

Claim Language	Mylan's ANDA Product

IV. THE '141 PATENT

Claim Language	Mylan's ANDA Product
<div data-bbox="203 760 776 1066" data-label="Text"> <p>[REDACTED]</p> </div> <div data-bbox="203 1087 812 1251" data-label="Chemical-Block"> <p>The chemical structure shows a central benzene ring connected via an amide linkage to a pyridine ring. The benzene ring has a trifluoromethyl (CF₃) group and a chlorine (Cl) atom. The pyridine ring has a methylcarbamoyl (NHMe) group. The structure is drawn in a horizontal orientation.</p> </div>	<div data-bbox="824 743 1393 1108" data-label="Text"> <p>[REDACTED]</p> </div> <div data-bbox="824 1129 1393 1579" data-label="Text"> <p>[REDACTED]</p> </div> <div data-bbox="824 1600 1334 1738" data-label="Text"> <p>[REDACTED]</p> </div> <div data-bbox="824 1768 1302 1873" data-label="Text"> <p>[REDACTED]</p> </div>

Claim Language	Mylan's ANDA Product
	<div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div>
<div>[REDACTED]</div>	<div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div>

Claim Language	Mylan's ANDA Product
	<div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div>
<div>[REDACTED]</div> <div>[REDACTED]</div>	<div>[REDACTED]</div> <div>[REDACTED]</div>

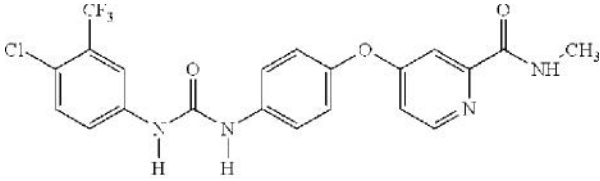
Claim Language	Mylan's ANDA Product
	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]

Claim Language	Mylan's ANDA Product
	<div>[REDACTED]</div> <div>[REDACTED]</div>
<div>[REDACTED]</div> <div>[REDACTED]</div> <div data-bbox="203 966 803 1144"><chem>CN(C)C(=O)c1cc(Oc2ccc(NC(=O)Nc3ccc(C(F)(F)F)c(Cl)c3)cc2)ccn1</chem></div>	<div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div>

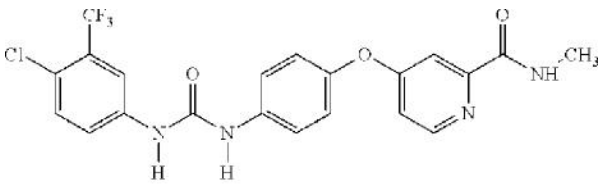
Claim Language	Mylan's ANDA Product
	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]

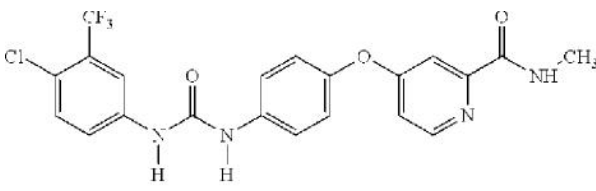
V. THE '330 PATENT

Claim Language	Mylan's ANDA Product
[REDACTED]	[REDACTED]
	[REDACTED]

Claim Language	Mylan's ANDA Product
<p data-bbox="203 296 708 369">[REDACTED]</p>  <p data-bbox="203 667 675 747">[REDACTED]</p>	<p data-bbox="824 289 1393 552">[REDACTED]</p> <p data-bbox="824 583 1382 1003">[REDACTED]</p> <p data-bbox="824 1031 1382 1224">[REDACTED]</p> <p data-bbox="824 1266 1382 1528">[REDACTED]</p> <p data-bbox="824 1539 1393 1766">[REDACTED]</p>
<p data-bbox="203 1793 760 1873">[REDACTED]</p>	<p data-bbox="824 1793 1382 1873">[REDACTED]</p>

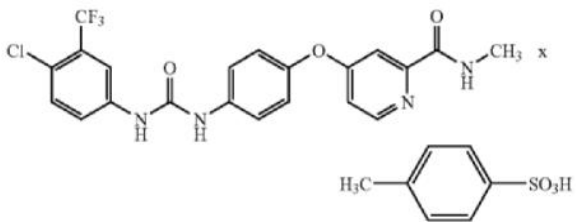
Claim Language	Mylan's ANDA Product
<div></div> <div></div> <div></div> <div>I</div>	<div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div> <div></div>

Claim Language	Mylan's ANDA Product
	<div></div>
<div></div> <div><chem>CN(C(=O)Nc1ccc(Oc2ccc(NC(=O)Nc3cc(Cl)cc(C(F)(F)F)c3)cc2)cc1)c4ccncc4</chem></div> <div></div>	<div></div> <div></div> <div></div> <div></div> <div></div> <div></div>

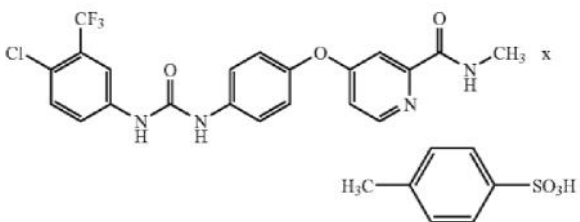
Claim Language	Mylan's ANDA Product
<p data-bbox="203 415 779 604">[REDACTED]</p> <div data-bbox="203 625 795 814"><chem>CC(=O)Nc1ccc(Oc2cc(C(=O)N)ncn2)cc1</chem></div> <p data-bbox="203 835 406 888">[REDACTED]</p>	<p data-bbox="820 415 1404 604">[REDACTED]</p> <p data-bbox="820 625 1388 1024">[REDACTED]</p> <p data-bbox="820 1045 1388 1318">[REDACTED]</p> <p data-bbox="820 1339 1372 1507">[REDACTED]</p> <p data-bbox="820 1528 1388 1801">[REDACTED]</p> <p data-bbox="820 1822 1396 1896">[REDACTED]</p>




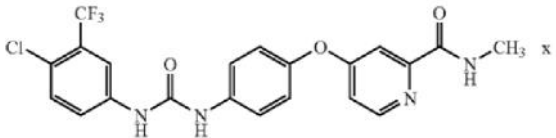
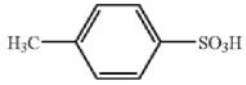
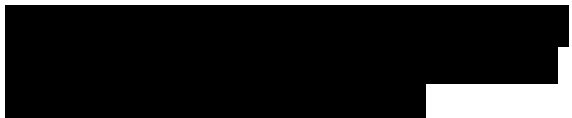

Claim Language	Mylan's ANDA Product

VI. THE '933 PATENT

Claim Language	Mylan's ANDA Product
<p>[REDACTED]</p> <p>(I)</p>  <p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p>
<p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p>

Claim Language	Mylan's ANDA Product
	
	  
	 

Claim Language	Mylan's ANDA Product
<p data-bbox="203 640 779 724">[REDACTED]</p> <p data-bbox="755 745 779 766">(I)</p> <div data-bbox="203 777 779 997"><p data-bbox="755 819 779 840">x</p></div> <p data-bbox="203 1092 779 1239">[REDACTED]</p>	<p data-bbox="820 630 1421 976">[REDACTED]</p> <p data-bbox="820 987 1421 1218">[REDACTED]</p>
<p data-bbox="203 1302 779 1449">[REDACTED]</p>	<p data-bbox="820 1302 1421 1491">[REDACTED]</p> <p data-bbox="820 1512 1421 1869">[REDACTED]</p>

Claim Language	Mylan's ANDA Product
	
 <p data-bbox="755 1365 779 1396">(I)</p>  <p data-bbox="730 1438 755 1459">x</p>  	

Claim Language	Mylan's ANDA Product
	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]
[REDACTED]	[REDACTED]
	[REDACTED]
	[REDACTED]

Claim Language	Mylan's ANDA Product
	<div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div> <div>[REDACTED]</div>
<div>[REDACTED]</div>	<div>[REDACTED]</div> <div>[REDACTED]</div>

Claim Language	Mylan's ANDA Product
	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]
	[REDACTED]

Claim Language	Mylan's ANDA Product
	
	
	
	
	

Claim Language	Mylan's ANDA Product
	
	

Claim Language	Mylan's ANDA Product
	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>
<p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p> <p>[REDACTED]</p>

Claim Language	Mylan's ANDA Product
	
	
	
	
	
	

Claim Language	Mylan's ANDA Product
	<p>[REDACTED]</p> <p>[REDACTED]</p>
<p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p>
<p>[REDACTED]</p>	<p>[REDACTED]</p> <p>[REDACTED]</p>

Claim Language	Mylan's ANDA Product
	
	
	



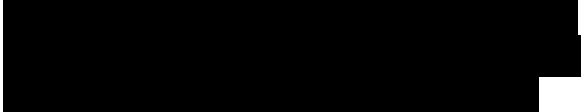
Claim Language	Mylan's ANDA Product
	<p>invalid claim. Mylan incorporates by reference Mylan's response to Interrogatory No. 3, and all supplemental responses thereto.</p> <p>Plaintiffs bear the burden of proof on the issue of infringement, and therefore Mylan's ANDA Products do not infringe this claim absent <i>prima facie</i> evidence of infringement. Any failure of proof on Plaintiffs' behalf would serve as an additional ground of noninfringement.</p>




SECOND SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 1:

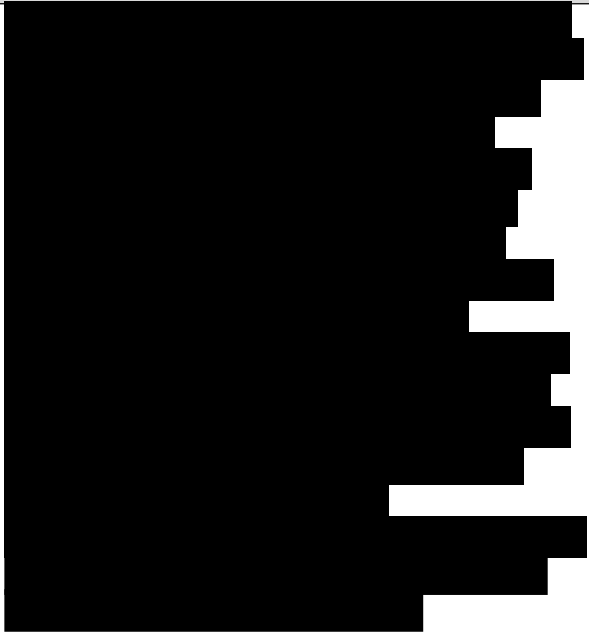

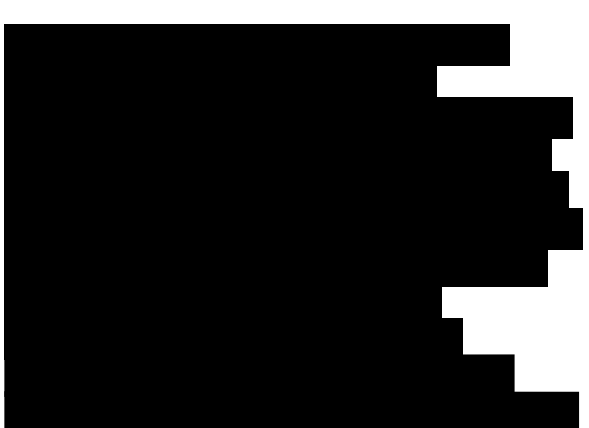
Mylan incorporates by reference the General Objections, Objections to Definitions and Instructions, and each specific objection set forth above as if fully stated herein. Mylan further incorporates by reference Defendant Mylan's First Supplemental Response to Interrogatory No. 1 as if fully set forth herein. Mylan supplements its response to Interrogatory No. 1 as follows:

Subject to the foregoing, Mylan's ANDA Products does not infringe claims 7-9 and 11 of the '141 patent for at least the following reasons:




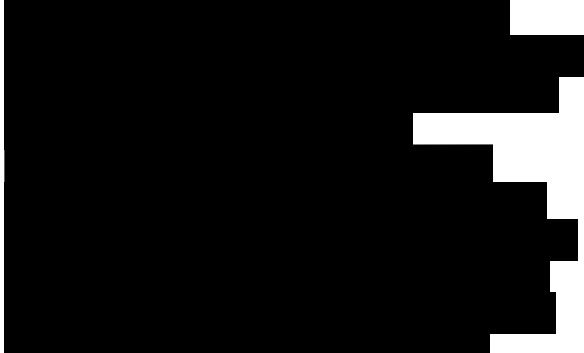
I. THE '141 PATENT

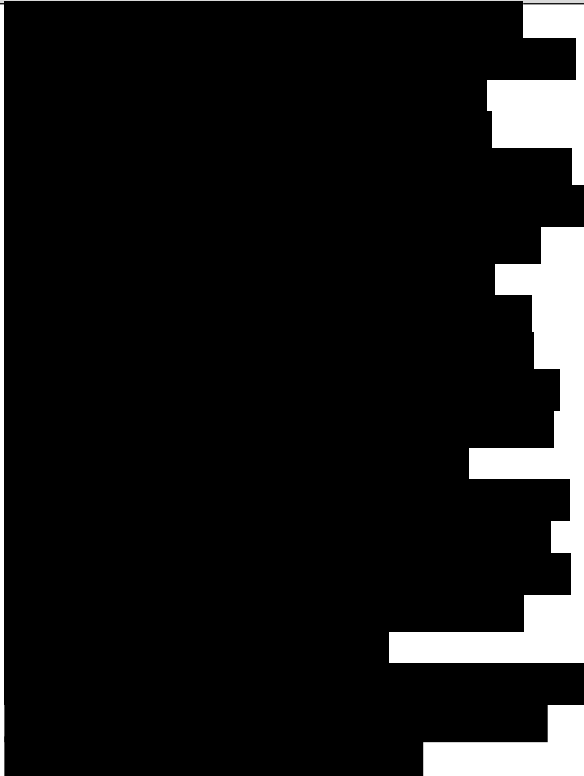


Claim Language	Mylan's ANDA Product
	 


Claim Language	Mylan's ANDA Product
	
	
	

Claim Language	Mylan's ANDA Product
	
	
	

Claim Language	Mylan's ANDA Product
	<div data-bbox="824 289 1404 552" style="background-color: black; height: 125px; width: 100%;"></div> <div data-bbox="824 577 1404 1056" style="background-color: black; height: 228px; width: 100%;"></div> <div data-bbox="824 1081 1404 1419" style="background-color: black; height: 161px; width: 100%;"></div>
<div data-bbox="203 1545 776 1734" style="background-color: black; height: 90px; width: 100%;"></div>	<div data-bbox="824 1545 1404 1839" style="background-color: black; height: 140px; width: 100%;"></div>

Claim Language	Mylan's ANDA Product
	
	
	
	

Claim Language	Mylan's ANDA Product
	
	
	

Claim Language	Mylan's ANDA Product
	
	
	
	

Claim Language	Mylan's ANDA Product

INTERROGATORY NO. 2:

Assuming that the use of Mylan's ANDA Product, including the use of such product in accordance with the proposed labeling (including the prescribing information and patient package insert) for such product, is determined to infringe each claim of the patents-in-suit and that each claim is determined to be valid and enforceable, do you contend that the manufacture, sale, offer for sale, or importation of Mylan's ANDA Product would not induce the infringement of one or more claims of the patents-in-suit? If your answer is that none of these actions would induce infringement, identify the claims you contend would not be infringed, all bases on which you contend any such claims would not be infringed, and all facts on which you rely for your contentions.

RESPONSE TO INTERROGATORY NO. 2:

Mylan incorporates the General Objections set forth above. Mylan objects to this interrogatory as overly broad, unduly burdensome, and oppressive to the extent it seeks information that is irrelevant to the claims and defenses at issue in this case and is not proportional to the needs of the case. For example, Mylan objects to the phrase "all bases" and "all facts" as being overly broad and requiring the production of trivial documents and other documents with limited, if any, relevance to the parties' claims or defenses. Mylan further objects to the phrases "each claim of the patents-in-suit," "any such claims," and "one or more claims" to the extent that this interrogatory seeks information not relevant to the Asserted Claims. Mylan will be responding to this interrogatory only insofar as it is relevant to the claims currently asserted by Plaintiffs. Mylan objects to this interrogatory to the extent it calls for a legal conclusion. Mylan further objects to this interrogatory as premature under the

Scheduling Order, as discovery is just beginning, Mylan has not received any discovery from Bayer, and no depositions have been conducted. Mylan further objects to this interrogatory as premature to the extent that Bayer has not established that Mylan's ANDA product would infringe each claim of the patents-in-suit, nor has there been any finding that each claim is valid and enforceable. Mylan further objects to this interrogatory to the extent that Mylan does not bear the burden of proof regarding infringement, including induced infringement. Mylan further objects to this interrogatory as premature under the Local Rules and the Default Standard for Discovery Including Discovery of ESI, which requires Plaintiffs to produce initial claim charts demonstrating how each product allegedly infringes each asserted patent claim before Defendants provide any initial contentions. This interrogatory essentially requires Mylan to provide non-infringement contentions before Plaintiffs have provided its infringement contentions. Mylan further objects to this interrogatory as seeking expert discovery prior to the dates for expert reports. Mylan objects to this interrogatory to the extent it seeks information that is confidential, protected by the right of privacy, and/or protected from disclosure by applicable privileges and protections, including without limitation the attorney-client privilege, work product protection, common interest privilege and/or consulting expert privilege. Mylan objects to this interrogatory to the extent it seeks information the disclosure of which is subject to third-party confidentiality obligations or a protective order. Mylan objects to this interrogatory to the extent it requests information not in Mylan's possession, custody, or control. Mylan objects to this interrogatory to the extent it calls for information already in Plaintiffs' possession, or calls for publicly available information. Mylan further objects to this interrogatory as improper under Fed. R. Civ. P. 33(a) because it purports to be a single interrogatory but contains multiple subparts. This interrogatory has at least three discrete subparts and is, therefore, at least three interrogatories. Mylan further objects to the description of this interrogatory as Interrogatory No. 2. Mylan considers this interrogatory to be Interrogatory Nos. 6-8.

Subject to and without waiving the foregoing objections, Mylan responds that it is Plaintiffs' burden to provide initial infringement contentions under the Scheduling Order. Mylan will supplement its response after Plaintiffs provide appropriate infringement contentions.

Discovery is on-going and Mylan will supplement its response if necessary and in accordance with the Federal Rules of Civil Procedure. Mylan is available to meet and confer with Plaintiffs to determine an appropriate discovery schedule for the provision of information, documents, and things in accordance with the Scheduling Order, Local Rules for the District of Delaware, the Default Standard for Discovery Including Discovery of ESI, and the Federal Rules of Civil Procedure.

SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 2:

Mylan incorporates by reference the General Objections, Objections to Definitions and Instructions, and each specific objection set forth above as if fully stated herein. This interrogatory is also premature and improper because it assumes that the Asserted Claims are valid and enforceable, which Mylan contends. Mylan supplements its response to Interrogatory No. 2 as follows:

The manufacture, sale, offer for sale, or importation of Mylan's ANDA Product would not induce the infringement of the Asserted Claims. As a matter of law, Mylan's ANDA Products cannot infringe invalid claims. *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983). The Asserted Claims are anticipated, obvious, indefinite, lacks written description, and/or not enabled. Mylan incorporates by reference its response and supplemental response to Interrogatory No. 1 for each of the Asserted Claims. Specifically, the documents cited by Plaintiffs do not establish facts necessary and sufficient to show induced or contributory infringement. For example, [REDACTED]

[REDACTED]

[REDACTED]

INTERROGATORY NO. 3:

Do you contend that any of the claims of the patents-in-suit are invalid? If your answer is anything other than an unequivocal “no,” state all bases for your contention and identify for each challenged claim all facts, documents, and circumstances on which you rely for your contention, including but not limited to an identification of the portion(s) of any statutes or legal doctrines under which you contend such claim is invalid and all bases for each such contention; the identification of any prior art or other references or information which you contend renders such claim invalid (either alone or in combination with other references or information); the identification, for each reference on which you rely, of what limitations of such claim are and are not disclosed by each reference and the portion(s) of each reference on which you rely for each limitation of the claim; and, to the extent you have an obviousness contention, the identification of the reference(s) that you contend should be modified or combined and all bases for your contention that there is a reason to modify the reference(s) and that there would have been a reasonable expectation of success.

RESPONSE TO INTERROGATORY NO. 3:

Mylan incorporates the General Objections set forth above. Mylan objects to this interrogatory as overly broad, unduly burdensome, and oppressive to the extent it seeks information that is irrelevant to the claims and defenses at issue in this case and is not proportional to the needs of the case. For example, Mylan objects to the phrase “all bases,” “all facts, documents, and circumstances,” and “any prior art or other references or information,” as being overly broad and requiring the production of trivial documents and other documents with limited, if any, relevance to the parties’ claims or defenses. Mylan further objects to the phrase “any of the claims” to the extent that this interrogatory seeks information not relevant to the Asserted Claims. Mylan will be responding to this interrogatory only insofar as it is relevant to the claims currently asserted by Plaintiffs. Mylan objects to this interrogatory to the extent it calls for a legal conclusion. Mylan further objects to this interrogatory as premature under the Scheduling Order, as discovery is just beginning, Mylan has not received any discovery from

Bayer, and no depositions have been conducted. Mylan further objects to this interrogatory as premature under the Local Rules and the Default Standard for Discovery Including Discovery of ESI, which requires Plaintiffs to produce initial claim charts demonstrating how each product allegedly infringes each asserted patent claim before Defendants provide any initial contentions. Mylan further objects to this interrogatory as seeking expert discovery prior to the dates for expert reports. Mylan objects to this interrogatory to the extent it seeks information that is confidential, protected by the right of privacy, and/or protected from disclosure by applicable privileges and protections, including without limitation the attorney-client privilege, work product protection, common interest privilege and/or consulting expert privilege. Mylan objects to this interrogatory to the extent it seeks information the disclosure of which is subject to third-party confidentiality obligations or a protective order. Mylan objects to this interrogatory to the extent it requests information not in Mylan's possession, custody, or control. Mylan objects to this interrogatory to the extent it calls for information already in Plaintiffs' possession, or calls for publicly available information. Mylan objects to this interrogatory as vague and ambiguous as to the phrases "portion(s)," "modified," "circumstances." Mylan proposes that the parties meet and confer to determine a meaning. Mylan objects to this interrogatory to the extent it includes multiple subparts, each of which constitutes a separate Interrogatory pursuant to Fed. R. Civ. P. 33(a)(1). Mylan further objects to this interrogatory as improper under Fed. R. Civ. P. 33(a) because it purports to be a single interrogatory but contains multiple subparts. This interrogatory has at least six discrete subparts and is, therefore, at least six interrogatories. Mylan further objects to the description of this interrogatory as Interrogatory No. 3. Mylan considers this interrogatory to be Interrogatory Nos. 9-14.

Subject to and without waiving the foregoing objections, and to the extent understood, Mylan responds that the answer to this interrogatory may be derived from Mylan's Notice Letters of November 9, 2015 and December 19, 2014, both of which are incorporated by reference herein. In addition to Mylan's Notice Letters of November 9, 2015 and December

19, 2014, Mylan further responds as follows: Claims 7-9 of the '141 patent claim a method of treating “a tumor of the kidney.” However, there are no examples, data or other information that would permit a person to practice the full scope of this claim without undue experimentation. Therefore, these claims are invalid for lack of enablement and written description under § 112(a).

Claim 35 of the '834 patent is directed to “[a] compound of Formula I: A—D—B or a pharmaceutically acceptable salt thereof, wherein D is —NH—C(O)—NH—, A is a substituted moiety of the formula: —L—M—L¹...” Neither the claim, written description, nor prosecution history of the '834 patent defines the value of “M.” Claims 36-38 depend from claim 35, and similarly fail to define the value of “M.” A person of ordinary skill in the art would be unable to make or use the claimed compound without knowing the complete identity of the compound. The lack of disclosure of “M” also does not allow the public to understand what chemical entity the inventor(s) claim as their invention. *General Electric Co. v. Wabash Appliance Corporation*, 304 U.S. 364 (1938) (“The inventor must ‘inform the public during the life of the patent of the limits of the monopoly asserted, so that it may be known which features may be safely used or manufactured without a license and which may not.”). Therefore, at least claims 35-38 of the '834 patent are invalid for lack of enablement and written description under § 112(a).

Claims 35-38 are also invalid for being indefinite, as these claims fail to particularly point out and distinctly claim the subject matter which the inventor(s) regard as the invention under § 112(b). *PPG Industries, Inc. v. Guardian Industries Corp.*, 75 F.3d 1558, 1562, 37 U.S.P.Q.2d 1618 (Fed. Cir. 1996) (“the language of the claims must make it clear what subject matter they encompass.”); *Technology Innovations, LLC v. Amazon.com, Inc.*, 2014 WL 1292093, *3-*5 (D. Del. 2014). Discovery is on-going and Mylan will supplement its response if necessary and in accordance with the Federal Rules of Civil Procedure. Mylan is available to meet and confer with Plaintiffs to determine an appropriate discovery schedule for the provision of information, documents, and things in accordance with the Scheduling Order,

Local Rules for the District of Delaware, the Default Standard for Discovery Including Discovery of ESI, and the Federal Rules of Civil Procedure.

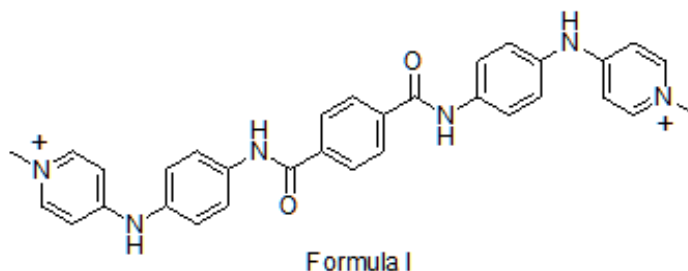
FIRST SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 4:

Mylan incorporates by reference the General Objections, Objections to Definitions and Instructions, and each specific objection set forth above as if fully stated herein. Mylan supplements its response to Interrogatory No. 3 as follows:

I. U.S. PATENT NOS. 7,235,576, 7,351,834, AND 7,897,623

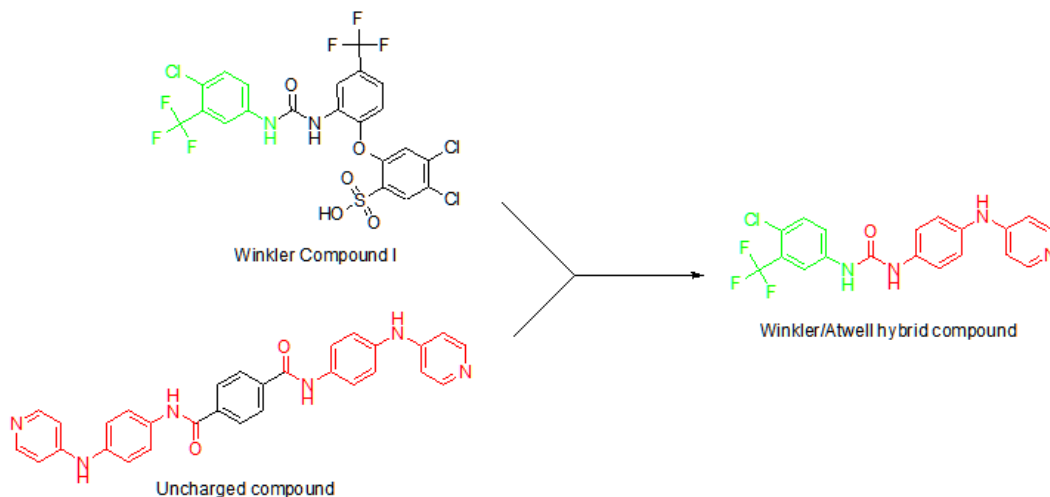
Plaintiffs have asserted claims 1-17 of the '576 patent, claims 1-8 of the '623 patent, and claims 39-41 of the '834 patent. The elements of these claims are described in the November 9, 2015 Notice Letter, which is incorporated by reference herein and also attached as Ex. B. *See* November 9, 2015 Notice Letter at 14-44. In addition to the noninfringement and invalidity defenses described in the November 9, 2015 Notice Letter, each of these claims are also rendered invalid for obviousness by Atwell *et al.*, Journal of Medicinal Chemistry (1968), 11(4), 690-4 ("Atwell"), in view of Winkler, in view of either Tang or Haga, and in further view of known solubility concerns.

Atwell describes anti-tumor compounds of Formula (I):

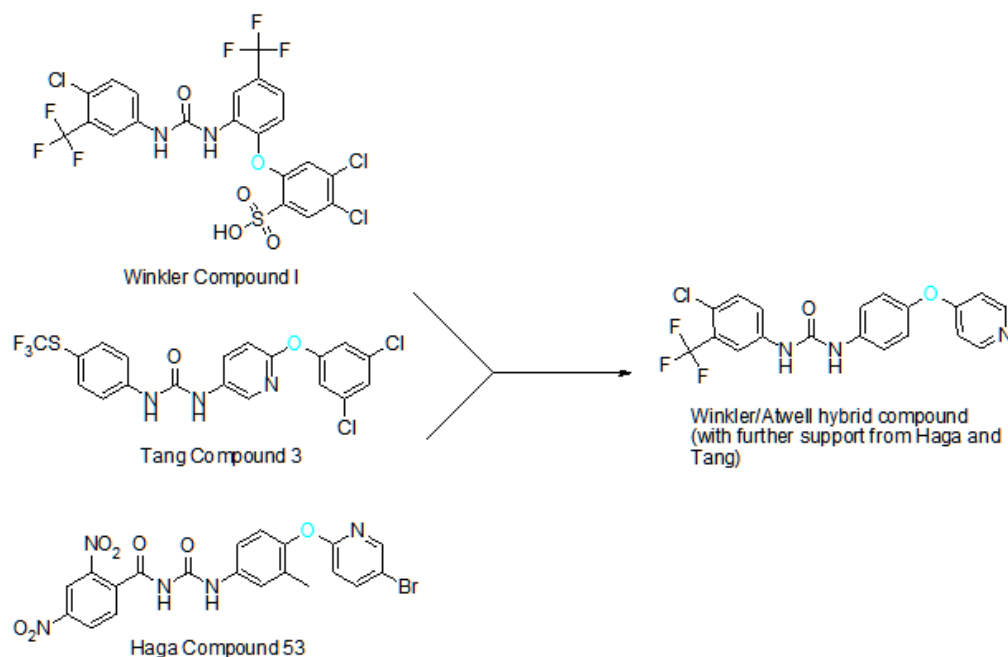


A POSA would understand that the relatively poor absorption of quaternary ammonium compounds from the lumen of the gastrointestinal tract limits their utility in therapy. *See, e.g.*

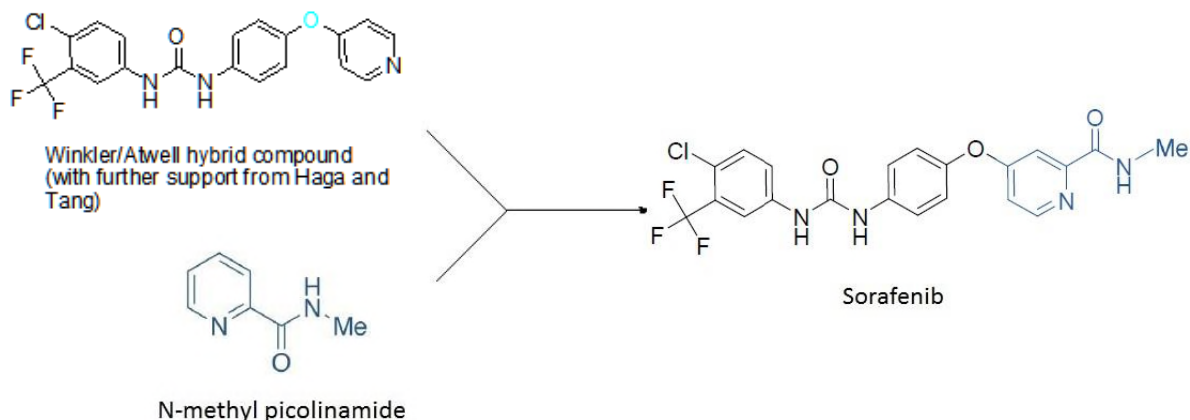
U.S. Patent No. 2,899,357, col. 1, ll. 20-50. Thus, the “uncharged compound” would be the obvious lead compound. Highlighted in red is the amine portion of the molecule that when combined with Compound I taught in Winkler (also described in detail in the November 9, 2015 Notice Letter) gives:



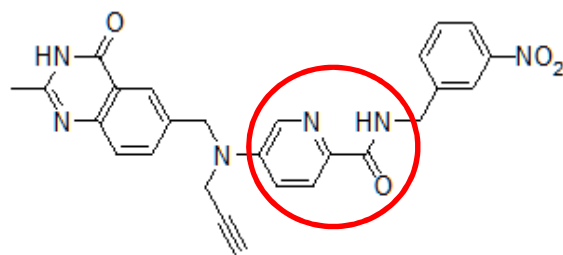
Furthermore, Winkler, Tang, and Haga, as described in the November 9, 2015 Notice Letter, teach preferred antitumor compounds with an ether linkage between the aryl/heteroaryl groups. Thus, a POSA in the art would be motivated to replace the amino linker with oxygen.



As further described in the November 9, 2015 Notice Letter, it was also known since at least September 5, 1989, that diphenyl ureas have poor solubility. Haga at col. 26, ll. 3-4, Compound 53. It was further known that nicotinamide and picolinamide have high solubility in water. N-methyl picolinamide, an obvious derivative of picolinamide, would be an obvious adduct to the Winkler/Atwell hybrid compound, which could be used by one of ordinary skill in the art to enhance the solubility of a anti-cancer drug while maintaining its potency and improving binding in an enzyme receptor pocket. Accordingly, incorporating N-methylpicolinamide into the Winkler/Atwell hybrid compound would enhance its solubility resulting in better bioavailability and also enhanced binding to the enzyme receptor pocket. The enhanced solubility provided by incorporating N-methylpicolinamide would result in the sorafenib structure. The resulting sorafenib structure, which has the N-methyl picolinamide shown in blue, is illustrated below:



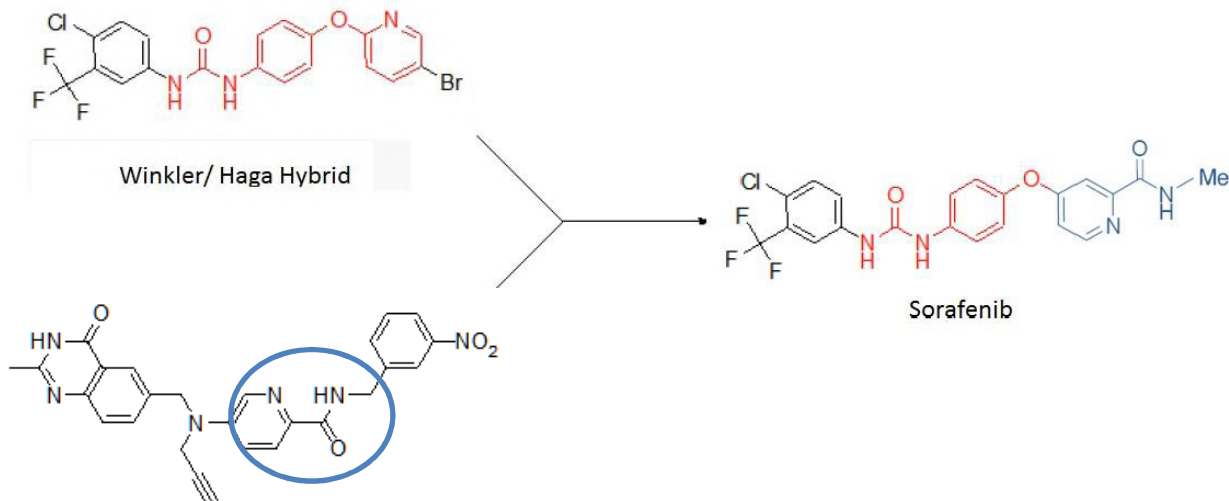
The pyridine-2-carboxamide substructure present in sorafenib is also disclosed in prior art relating to other pharmaceutical agents. U.S. Patent No. 5,252,573 (“the ’573 patent”), filed on November 18, 1991, and issued on October 12, 1993, relates to quinazoline derivatives, or pharmaceutically acceptable salts thereof, which possess anti-tumor activity, their manufacture, and pharmaceutical compositions containing them. ’573 patent at col. 21, ll. 26-68. Example 4 of the ’573 patent discloses 5-[N-(3,4-dihydro-2-methyl-4-oxoquinazolin-6-ylmethyl)-N-(prop-2-ynyl)amino]-N-(3-nitrobenzyl)pyridine-2-carboxamide (Example 4, col. 31, ll. 5–39), as a preferred compound (col. 9, l. 32) and specifically claims this compound (Claim 5):



Therefore, the ’573 patent, which relates to compounds known to possess anti-tumor activities, and which presents Example 4 as a preferred compound, would render obvious 1-17 of the ’576 patent, claims 1-8 of the ’623 patent, and claims 39-41 of the ’834 patent, by motivating a POSA to incorporate the pyridine-2-carboximide substructure with the lead compounds described previously.

For example, the Winkler/Haga hybrid compound (*see* November 9, 2015 Notice Letter at 74-75) in view of the preferred compound disclosed as Example 4 in the ’573 patent renders

obvious 1-17 of the '576 patent, claims 1-8 of the '623 patent, and claims 39-41 of the '834 patent:

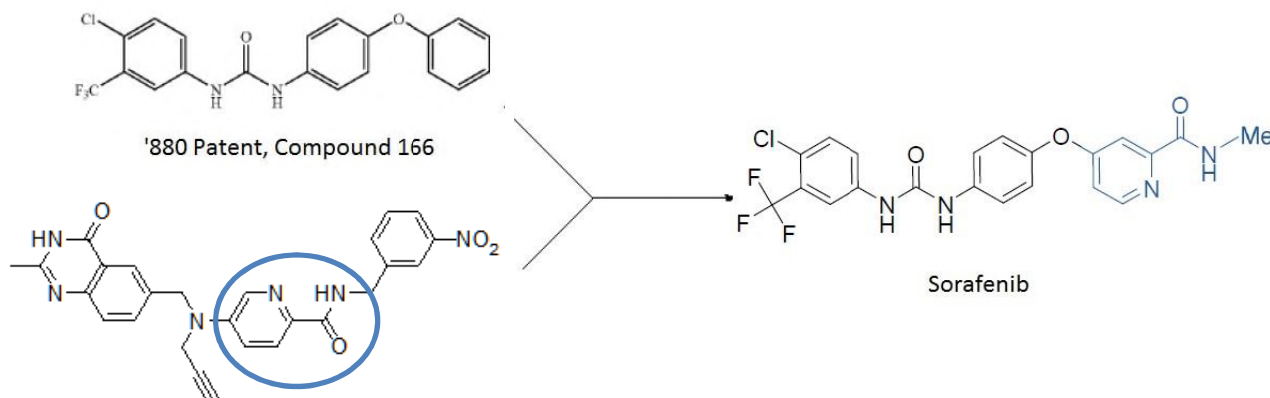


'573 patent at Example 4, col. 31, ll. 5 – 39

Similarly, the Winkler/Armistead hybrid compound (*see* November 9, 2015 Notice Letter at 76-77) in view of the preferred compound disclosed as Example 4 in the '573 patent renders obvious 1-17 of the '576 patent, claims 1-8 of the '623 patent, and claims 39-41 of the '834 patent:

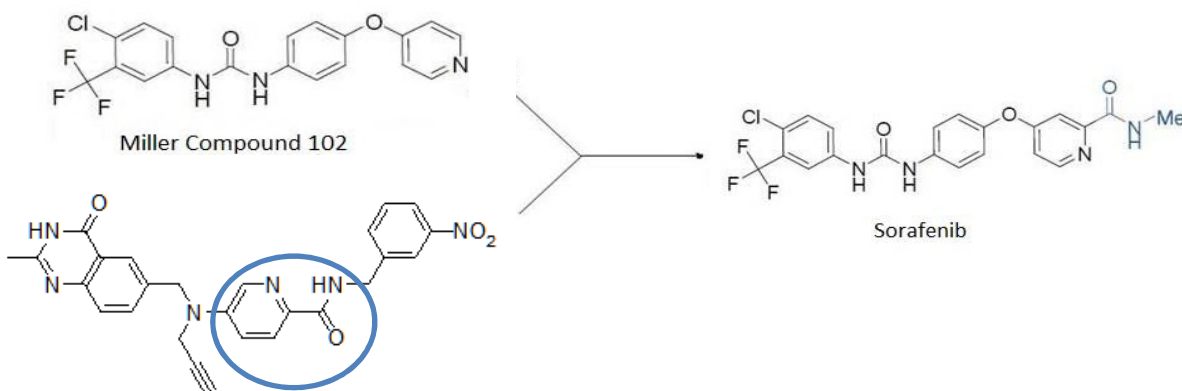
Similarly, Compound 102, as disclosed in the '265 Publication (*see* November 9, 2015 Notice Letter at 78-79) in view of the preferred compound disclosed as Example 4 in the '573 patent renders obvious 1-17 of the '576 patent, claims 1-8 of the '623 patent, and claims 39-41 of the '834 patent:

Similarly, Compound 166, as disclosed in the '880 patent (*see* November 9, 2015 Notice Letter at 80-81) in view of the preferred compound disclosed as Example 4 in the '573 patent renders obvious 1-17 of the '576 patent, claims 1-8 of the '623 patent, and claims 39-41 of the '834 patent:



'573 patent at Example 4, col. 31, ll. 5 – 39

A POSA would consider it obvious to modify Compound 102 as disclosed in Miller PCT to incorporate the pyridine-2-carboximide substructure in light of the disclosure of Compound 101, as disclosed in Dumas. *See* November 9, 2015 Notice Letter at 95-97. Example 4 of in the '573 patent provides further support to add this substructure and to render claims 1-17 of the '576 patent obvious:



'573 patent at Example 4, col. 31, ll. 5 – 39

II. U.S. PATENT NO. 8,841,330

The elements of claims 4, 10, 13, and 14 of the '330 patent ("the '330 Asserted Claims") are described in the November 9, 2015 Notice Letter. *Id.* at 46-48. Each of the '330 Asserted Claims claim sorafenib or its tosylate salt. Thus, this element of each of the '330 Asserted Claims is not novel or is obvious. Accordingly, Defendants incorporate by reference the arguments set forth above for the '576 patent, the '834 patent, and the '623 patent. Additionally, as described in the November 9, 2015 Notice Letter, claims 4, 10, 13, and 14 are invalid under § 112 for lacking adequate written description and enablement. November 9, 2015 Notice Letter at 111-15. Each of these claims is also rendered invalid for obviousness by the '265 Publication and/or Dumas alone or in combination with one another.

The '265 Publication was published on October 30, 2008, from U.S. Application Serial No. 12/145,679 as a continuation of application Serial No. 09/776,936 filed on December 22, 1998. The '265 Publication describes symmetrical and unsymmetrical substituted diphenyl ureas useful for the treatment of a cancerous cell growth mediated by raf kinase. As discussed above, the prior art renders the sorafenib compound obvious. Additionally, the '265 Publication teaches that the use of such compounds are "useful in pharmaceutical compositions for human

or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf kinase.” ’265 Publication at [0003]. Additionally, it explicitly states that the “compounds of the invention are useful in treating solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder, or colon” *Id.* The ’265 Publication additionally discloses a “method for the treatment of a cancerous cell growth.” *Id.* at [0020]. It also discloses that the “daily oral dosage regimen will be preferably be from 0.01 to 200 mg/kg of total body weight, thereby discloses the “effective amount” of claims 1 and 13. *Id.* at [0069]. Further the ’265 Publication provides various “administration” techniques along with the recommended dose. *Id.*

Published on July 1, 1999, and having an international filing date of December 22, 1998, Dumas claims priority to U.S. Application Serial No. 08/996,343 filed on December 22, 1997. Dumas discloses “[m]ethods of treating tumors mediated by raf kinase, with substituted urea compounds.” Dumas at Abstract. In particular, it teaches that such compounds are “useful in treating solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon).” Dumas at 2:11-14. Like the ’265 Publication, Dumas also provides methods for administering and preferred dosage amounts. *Id.* at 27:20-30.

Each and every claim limitation of the ’330 patent is met by both Dumas and the ’265 Publication as discussed above. Thus, Asserted Claims 4, 10, 13, and 14 of the ’330 patent are invalid as obvious over the ’265 Publication or Dumas alone or in combination with one another.

III. U.S. PATENT NO. 8,618,141

Plaintiffs have asserted claims 7-9 and 11 of the ’141 patent. The elements of those claims are described in the December 19 2014 Notice Letter (“the ’141 Notice Letter”), incorporated by reference herein and also attached as Ex. A. ’141 Notice Letter at 11, 21, 23.

Each of these claims are invalid as anticipated by '012 Publication under 35 U.S.C. § 102(b). The preamble of claim 7 of the '141 patent should not be construed as a limitation; however, even if it is, the claim would nevertheless be anticipated. The preamble states “a method of blocking tumor angiogenesis in a human or other mammal” Claim 7. Sorafenib’s biochemical property of blocking tumor angiogenesis through KDR (VEGFR-2) inhibition as disclosed in the '141 patent is an inherent property. Thus, sorafenib would “block tumor angiogenesis” every time that sorafenib is used to treat a tumor in a patient.

By the time of the filing of the application that lead to the '141 patent, the method of treating patients with tumors by administration of sorafenib tosylate was known. It was also known that tumor angiogenesis was a “prerequisite” for the substantive growth of tumors. *See* '141 patent, 2:1-2. The '141 patent discloses that sorafenib inhibits KDR (VEGFR-2). Inhibition of KDR (VEGFR-2) blocks angiogenesis. John K. Buolamwini, “Novel Anticancer Drug Discovery,” *Curr. Opin. Chem. Biol.* Aug. 1999, 3(4):500-09 (“Buolamwini”) at 502, 505-06. Thus, the prior art method of administering sorafenib tosylate to patients with tumors necessarily blocked tumor angiogenesis by inhibiting KDR (VEGFR-2).

Here, the method disclosed by the prior art was the administration of sorafenib to patients having solid tumors. The “natural and inherent results” of that method are the inhibition of tumor growth by inhibition of Raf kinase (recognized result) and the inhibition of angiogenesis by the inhibition of KDR (VEGFR-2) activity (unrecognized result). The '141 patent claims the exact method disclosed in PCT Publication No. WO 00/42012 to Riedl et al. (“the '012 publication”), which was published on July 20, 2000 and is thus 102(b) prior art to the '141 patent; the administration of sorafenib to patients results in the particular benefits of Raf inhibition and KDR inhibition. *See Perricone v. Medicis Pharm. Corp.*, 432 F.3d 1368,

1378 (Fed. Cir. 2005) (for a reference to anticipate a method claim inherently, the prior art must first “disclose[] the very same methods, then the particular benefits must naturally flow from those methods even if it is not recognized at the time . . .”). Thus, claims 8 and 9 are anticipated regardless of whether the preamble is considered to be a limitation of the claims.

Furthermore, the '012 publication specifically discloses the pharmaceutical composition to have a “daily oral dosage regimen” to “preferably be from 0.01 to 200 mg/Kg of total body weight.” '012 publication at 12:31-32. Thus, claim 11 is expressly anticipated by the '012 publication.

For at least these reasons, claims 7-9 and 11 of the '141 patent are invalid as anticipated by the '012 publication under 35 U.S.C. § 102(b).

Claim 7 of the '141 patent is invalid either as anticipated under 35 U.S.C. § 102 over the '012 publication or as obvious under 35 U.S.C. § 103(a) over the '012 publication, in view of Rika Hoshino et al., “Constitutive activation of the 41-/43-kDa mitogen-activated protein kinase signaling pathway in human tumors,” *Oncogene* Jan. 21, 1999, 18:813-22 (“Hoshino”). As discussed above, the '012 publication discloses that sorafenib is useful in treating solid tumors, providing non-limiting examples of lung, pancreas, thyroid, bladder, and colon tumors. '012 publication at 2:18-20. Claim 7 of the '141 patent recites a method of blocking tumor angiogenesis in a tumor of the kidney comprising administering sorafenib. A person of ordinary skill in the art would recognize that a kidney tumor is a solid tumor and that the '012 publication's disclosure of the treatment of solid tumors would encompass the treatment of a kidney tumor. This would render claim 7 invalid as anticipated under 35 U.S.C. § 102(b), as articulated above.

Claims 7 and 11 are invalid as obvious under 35 U.S.C. § 103(a) over the '012 publication in view of Hoshino. From the '012 publication, one of skill in the art would know that sorafenib could be administered to patients having solid tumors and the effective amount to be administered, as detailed above and in the '141 Notice Letter. One of skill in the art would also know that sorafenib could be formulated as a tosylate salt for oral administration. Finally, the skilled artisan would know that sorafenib tosylate would act as a raf inhibitor to combat cancerous tumors. One of skill in the art, who would be an experienced scientist familiar with medicinal chemistry, biochemical pathways involved with cancer, and anti-cancer therapies, would recognize that sorafenib tosylate would be an effective treatment of any cancer in which Raf was implicated. Hoshino identifies kidney cancer as one such cancer. Hoshino at 815. Specifically, Hoshino shows that MAP kinases are overactive in human kidney tumors. *Id.* Hoshino also demonstrates that MEK and raf activation are responsible for that elevated MAP kinase activity. *Id.* at 815-16; Table 4. Knowing that sorafenib was an inhibitor of raf and effective in treating solid tumors from the '012 publication, it would be obvious for one of skill in the art to employ sorafenib in the treatment of kidney tumors (a type of solid tumor). Accordingly, claims 7 and 11 would be obvious under 35 U.S.C. § 103(a) to one of skill in the art over the '012 publication in view of Hoshino.

Claims 8 and 9 of the '141 patent are also obvious over the '012 publication in view of Buolamwini. Claim 8 depends on claim 7, and further states “wherein the tumor of the kidney that is treated is characterized by abnormal angiogenesis or hyperpermiability processes, which are neither raf-mediated nor p38-mediated.” Claim 9 reads: “A method as in Claim 8 wherein the tumor of the kidney that is treated is characterized by abnormal angiogenesis or hyperpermiability processes, which are mediated by KDR (VEGFR-2).” As discussed above, the

inhibition of abnormal angiogenesis mediated by KDR (VEGFR2) is a natural outcome of the administration of sorafenib disclosed by the '012 publication.

One of skill in the art would know that sorafenib inhibited Raf kinase, and that its administration to patients would be an effective treatment for solid tumors. *See* discussion above. One of skill in the art would also know that Raf is activated with KDR (VEGFR-2)-mediated tumor angiogenesis. *See* Buolamwini at 501-504. Accordingly, it would be obvious for one of skill in the art to use sorafenib to inhibit KDR (VEGFR-2)-mediated angiogenesis by inhibiting Raf—an enzyme involved in VEGF's angiogenic effects. Accordingly, claims 8 and 9 are invalid as obvious under 35 U.S.C. § 103(a) over the '012 publication and Buolamwini.

For at least these reasons, claims 7-9 and 11 of the '141 patent are invalid as obvious under 35 U.S.C. § 103(a) over the prior art. Mylan reserves the right to supplement these initial invalidity contentions to substitute other references to combine and/or to identify motivations to combine particular references with one another with additional particularity.

In addition, claims 7-9 and 11 of the '141 patent are invalid in view of the doctrine of obviousness-type double patenting. The double patenting doctrine is designed to prevent “unjustified timewise extension of the right to exclude.” *In re Van Ornum*, 686 F.2d 937, 943-44 (C.C.P.A. 1982). For instance, the doctrine bars an applicant from obtaining separate patents with separate terms for both a product and process for making that product, unless the product and process are “patentably distinct.” *See In re Taylor*, 53 C.C.P.A. 1187, 360 F.2d 232, 234 (1966); *In re Cady*, 22 C.C.P.A. 1190, 77 F.2d 106, 109 (1935) (instructing that “double patenting is not sustainable when the product can be fabricated by processes other than that secured by the issued process patent”) (quotation marks omitted).

Claims 7-9 and 11 of the '141 patent are invalid under the doctrine of obviousness-type double patenting over claims 1, 7, 13, and 14 of U.S. Patent No. 8,841,330 ("the '330 patent"). Claim 1 of the '330 patent recites a method for the treatment of a tumor of the prostate, breast, liver, ovary or cervix in a human or animal comprising administering an effective amount of sorafenib or a pharmaceutically acceptable salt thereof. Claim 7 of the '330 patent claims the same method as claim 1, but uses the tosylate salt of sorafenib. Claims 13 and 14 of the '330 patent are similar to the claims 1 and 7 respectively, except claims 13 and 14 are limited to the treatment of liver cancer. Claims 7-9 and 11 of the '141 patent are invalid under the doctrine of obviousness-type double patenting because the differences between the Asserted Claims in the '141 patent and the claims of the '330 patent are not patentably distinct. The '141 patent merely claims an inherent and/or obvious variant of the '330 claims—treating kidney tumors (claims 7, 8, 9 and 11) and merely restates the effective amount of sorafenib to be "0.01 to 200 mg/kg of total body weight" (claim 11), which is inherent and obvious in light of claims 1, 7, 13, and 14 of the '330 patent, which recite a method for administering sorafenib (or its tosylate salt) in an "effective amount." Treating kidney tumors is inherent and/or an obvious variant of the '330 patent because as mentioned above, treating KDR-mediated tumors is a natural outcome of administering sorafenib in an "effective amount." Thus, claims 7-9 and 11 of the '141 patent are invalid under the doctrine of obviousness-type double patenting over claims 1, 7, 13, and 14 of the '330 patent because the claims are not patentably distinct and only serve to extend the exclusive rights granted to Plaintiffs by the '330 patent.

Claims 7-9 and 11 are also invalid under the doctrine of obviousness-type double patenting in view of claims 1, 6, 8, and 13 of U.S. Patent No. 8,124,630 ("the '630 patent"). Claim 1 of the '630 patent recites a "method for treatment of carcinoma of the lung, pancreas,

thyroid, bladder or colon in a human or animal in need thereof comprising administering an effective amount of [sorafenib] . . . or a pharmaceutically acceptable salt thereof.” Claim 6 depends from claim 1 and claims a method for the treatment of carcinoma of the bladder in a human in need thereof. Claim 8 mirrors claim 1 using the tosylate salt of [sorafenib]. Claim 13 depends from claim 8 and claims a method for the treatment of carcinoma of the bladder. Similar to the analysis above with respect to the ’330 patent, claims 1, 6, 8, and 13 of the ’630 patent render the claims of the ’141 patent obvious. Thus, claims 7-9 and 11 of the ’141 patent are invalid under the doctrine of obviousness-type double patenting.

Claim 11 of the ’141 patent claims a method of blocking angiogenesis in “a tumor of the kidney.” As discussed in the Response to Interrogatory No. 3 above, there are no examples, data or other information that would permit a person to practice the full scope of this claim without undue experimentation. Therefore, these claims are invalid for lack of enablement and written description under § 112(a).

Claims 8 and 9 of the ’141 patent are invalid under 35 U.S.C. § 112 because they lack sufficient written description because the ’141 patent does not contain any description of tumors that possess “abnormal angiogenesis or hyperpermiability processes that are not p38-mediated or raf-mediated.” *See also* ’141 Notice Letter at 23-24.

Claims 8 and 9 of the ’141 patent are invalid under 35 U.S.C. § 112 because the phrase “hyperpermiability processes” is indefinite.

Claims 8 and 9 of the ’141 patent are also indefinite for lacking antecedent basis. Claim 8 depends from claim 7. Claim 7 never recites a tumor of the kidney “that is treated,” thus, claim 8 lacks antecedent basis. Claim 9 depends from claim 8, thus claim 9 suffers a similar fate.

IV. U.S. PATENT NO. 8,877,933

Plaintiffs have asserted claims 1-4, 8-10, 16-21, and 27-31 of the '933 patent. These claims generally are directed to sorafenib tosylate Polymorph I, compositions containing it, or methods of using it. The elements of these claims are described in the November 9, 2015 Notice Letter, which is incorporated by reference herein and also attached as Ex. B.

Polymorph I is described in the '933 patent as the most stable form of sorafenib tosylate at room temperature. The '933 patent reports that sorafenib tosylate can exist in the following physical forms: three polymorphs (Polymorph I, II and III) and two solvates (monomethanol solvate and monoethanol solvate).

According to the data presented in the '933 patent, metastable Polymorph II and Polymorph III will convert to Polymorph I upon heating, such as during the course of differential scanning calorimetry (DSC). Similarly, the two known solvates will desolvate and ultimately convert to Polymorph I by heating.

Sorafenib tosylate is admitted prior art to the '933 patent. The '933 patent states "sorafenib tosylate is disclosed in the prior art in WO 03/068228" ("WO 228") which was published more than one year before the priority date of the '933 patent and is therefore prior art under at least 35 U.S.C. § 102(b). WO 228 claim 22 specifically discloses sorafenib tosylate and a method of using it: "A method of treating disease mediated by VEGF-induced signal transduction pathway comprising administering N-(4-chloro-3-(trifluoromethyl) phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl) urea tosylate." WO 228 discloses sorafenib tosylate free base and a method of making it as Example B. It also discloses 4-toluene sulfonic acid as a potential salt-forming acid. WO 228 at 15.

During the opposition to the European correspondent of the '933 patent, Plaintiffs agreed that WO 228 is the closest prior art.

According to the '933 patent, the applicant prepared sorafenib tosylate "according to a general standard method for the preparation of tosylate salts, as described in example 1 of the

working examples. In this method [sorafenib] is obtained in one crystal polymorph which is referred to below as polymorph II.” ’933 patent at 2:14-18.

During the prosecution of the European counterpart of the ’933 patent the applicant wrote:

Usually the preparation of a salt of a known compound follows a standard procedure which is e.g. solving the base and the acid in a solvent and let the resulting salt crystalizing as described in Example 1 of the present application. According to such a protocol the tosylate salt mentioned in [the WO ’228 publication] can be prepared and that was initially done in our laboratories. The result was that [sorafenib tosylate] was obtained in the metastable polymorph II. That means the standard procedure yields [sorafenib tosylate] in the metastable polymorph II.

MYL_SOR00011393.

The method specifically disclosed in the ’933 patent is:

Example 1

4-{4-[[{4-Chloro-3-(trifluoromethyl)phenyl}amino}carbonyl]amino]phenoxy}-N-methylpyridine-2-carboxamide tosylate in the polymorph II

903 g of 4-{4-[[{4-chloro-3-(trifluoromethyl)phenyl}amino}carbonyl]amino]phenoxy}-N-methyl-pyridine-2-carboxamide, prepared as described in WO 00/42012, are initially charged in 2700 ml of ethanol. 451.7 g of p-toluenesulfonic acid monohydrate are dissolved in 1340 g of ethanol and added dropwise at room temperature. The suspension is stirred at room temperature for 1 hour, then filtered off with suction, and the residue is washed three times with 830 ml each time of ethanol. The drying is effected at 50° C. under reduced pressure with supply of air. 1129.6 g of the title compound in the polymorph II are obtained.

’933 patent at 13:35-53.

Tosylate salts and methods preparing them were known in the prior art. *See, e.g.,* P. HEINRICH STAHL ET AL., HANDBOOK OF PHARMACEUTICAL SALTS 309-10 (2002); U.S. Patent No. 5,659,030 (crystalline cephalosporin tosylate salt); Numerous prior art reference disclose tosylate salts and methods of making them, such as U.S. Patent No. 3,065,136 (itrimin tosylate); U.S. Patent. No. 4,831,025 (sultamicillin tosylate); U.S. Patent No. US6093814 (cefdinir tosylate); WO2004072085A2 (clopidogrel tosylate); U.S. Patent No. 6,608,206 (S(-

)Amlodipine tosylate); U.S. Patent No. 7,094,930 (sertraline tosylate); WO 2002/030900A (Non-deliquescent salt of 4-hydroxypiperidine derivative). *See also* Piotr Milart & Katarzyna Stadnicka, *Salts of 4-(2,4,6-Triphenyl-1-pyridinio)phenolate with p-Toluenesulfonic Acid in Molar Ratio 1:1 and 2:1 – Crystal and Molecular Structure*, Eur. J. Org. Chem 2001, 2337-2441 (2001); C.R. Noller & Poe Liang, *Para-Toluene Sulfonates as Derivatives for the Identification of Aromatic Amines*, 54 J. SOC. CHEM. IND. 670 (Feb. 1932); H.K. Hall, Jr., *Steric Effects on the Base Strengths of Cyclic Amines*, THIS JOURNAL, 5444 (May 1957).

Foreign correspondents of the '933 patent have issued in various jurisdictions. At least the European and Indian correspondents have been subject to opposition proceeding.

MYL_SOR11142 -MYL_SOR00015259.

During the Indian and European oppositions of the corresponding patents, the opponents reported that all of their attempts to prepare Polymorph II according to the method disclosed in the '933 patent have failed. *See, e.g.*, MYL_SOR00012211. The disclosed method invariably produces Polymorph I. *Id.* According to Plaintiffs during the European Opposition proceedings these results are explainable because, Polymorph II is a “disappearing polymorph.” MYL_SOR00012210.

Various Asserted Claims include limitations to PXRD reflections, IR spectrum peak maximum, Raman spectra peak maximum, and melting point of Polymorph I. These are inherent properties of Polymorph I and therefore they add nothing to the claims for purposes of the invalidity analysis. The mere existence of Polymorph I would inherently produce a crystal form of sorafenib tosylate with the recited PXRD reflections, IR spectrum, a peak maximum, Raman spectra peak maximum, and melting point of Polymorph I. As a result, they add nothing to the invalidity analysis of these claims. *See, e.g.*, Stephen S. Zumdahl, *Chemistry*, D.C. Heath and Company, Lexington, MA, p. 390-93 (1986).

A. ANTICIPATION

1. Inherent Anticipation Due to a “Disappearing Polymorph”

As noted above, according to information presented in the European and Indian oppositions, attempts to make sorafenib tosylate Polymorph II according to the method presented in the '933 patent have invariably resulted in the formation of Polymorph I.

All reported attempts by a POSA to make sorafenib tosylate by any of the typical methods for making tosylate salts as of the priority date would have resulted in Polymorph I. Similarly, on information and belief, attempts in the present to prepare Polymorph II by any such standard method would have resulted in the discovery of the most stable polymorph at room temperature, i.e., Polymorph I.

Attempts by a POSA to make sorafenib tosylate by any of the typical methods for making tosylate salts as of the priority date would have resulted in Polymorph I. Numerous prior art reference disclose tosylate salts and methods of making them..

Polymorph II would have converted to Polymorph I under ordinary conditions, including ordinary pharmaceutical storage conditions. Polymorph I therefore is inherently anticipated. *See SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331 (Fed. Cir. 2005).

For the foregoing reasons, each of the Asserted Claims directed to sorafenib tosylate Polymorph I and its inherent properties are anticipated (e.g. Claims 1-4 and 27-31)

Even if Asserted Claims of the '933 patent are not anticipated, they are obvious over the prior art for at least the reasons stated in the November 9, 2015 Notice Letter, *id.* at 104-10, as well as for reasons set forth below.

2. Inherent Anticipation (or Obviousness) by Standard Analytical Techniques

Regardless of the physical form of sorafenib tosylate produced through the preparation of the salt (e.g. Polymorph II), a POSA would have conducted standard analytical techniques on the compound. Many of these techniques would have produced Polymorph I. For example, a POSA would have used any of the standard techniques to take a melting point of sorafenib

tosylate, or a similar technique (DSC, hot bar, TGA, etc.) that would have inevitably produced Polymorph I.

WO 228 reports the melting point of compounds exemplified in the patent. A POSA would have understood this as an instruction to take the melting point of any compound within the scope of the patent that a POSA prepared, including sorafenib tosylate.

According to the data in the '933 patent, every known form crystalline form of sorafenib tosylate will convert to Polymorph I in the course of conventional analytical techniques. For example, based on the data presented in the patents, taking the melting point or DSC of Form 2 under ordinary conditions would have inevitably resulted in Form 1.

To the extent that this does not constitute anticipation, it would render the Asserted Claims obvious. A POSA would have been motivated to use these standard techniques in analyzing any form of sorafenib tosylate, even if the POSA were not specifically searching for other physical forms of sorafenib tosylate. For example, taking a melting point is almost invariably one of the first steps in characterizing a new compound.

For example, Giron (2004) states:

The melting point of organic substances is one of the first properties measured. A number of techniques are available, from immediate melting to the capillary method described in various pharmacopoeias. The substance is heated and the transition to the liquid phase is observed visually or by hot-stage microscopy. Generally the melting point is measured by DSC. Some polymorphs may have differences of melting points less than 1°C or differences more than 100°C

Giron, D et al, "Solid-State Pharmaceutical Compounds, Impact of the ICH Q6 guidance on industrial development", *Journal of Thermal Analysis and Calorimetry* 77: 709-747 (2004).

To the extent a POSA's attempts to prepare sorafenib tosylate did not initially produce Polymorph I, the use of any of these and other standard analytical techniques would have inevitably produced Polymorph I, rendering the Asserted Claims anticipated or obvious.

3. Anticipation by Public Use

Each of the Asserted Claims of the '933 patent also are invalid as anticipated or obvious due to public use in the United States before the earliest claimed priority date. ■■■

[REDACTED]
[REDACTED] Therefore, each of the Asserted Claims is anticipated or obvious.

B. Obviousness

Each of the Asserted Claims of the '933 patent is invalid as obvious over the prior art described above and in this section. To the extent that the Asserted Claims are not rendered anticipated or obvious as described above, the Asserted Claims are nevertheless obvious.

A POSA would have been strongly motivated to identify the most stable form of sorafenib tosylate, would have had a reasonable expectation of success in doing so, and would have selected that most stable form for pharmaceutical development and use.

1. Scope and Content of the Prior Art

The scope and content of the prior art, as well as the differences between the claims and the prior art, is described above in, e.g., the sections describing the background of the patent and anticipation. The scope and content of the prior art, as well as differences between the claims and prior art, is further described below.

2. Motivation to Identify the Most Stable Form and Expectation of Success in Obtaining the Most Stable Polymorph

A POSA as of the priority date would have been strongly motivated to investigate crystal forms of sorafenib tosylate and, in particular, identify the most stable form. *See Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances*, FOOD AND DRUG ADMINISTRATION (February 1987). As of the priority date, sorafenib tosylate was a drug undergoing clinical development and Plaintiffs were seeking approval to market it as a drug for human use in the United States and other countries.

During the prosecution of the corresponding European patent, Plaintiffs stated:

It is very important for a pharmaceutical product to have always the same constant properties. Therefore there is a need to find the most stable form of a compound because only the most stable form can ensure that all properties and characteristics regarding stability, solubility, shelf life and bioavailability maintain constant during manufacturing, storage and administration. . . .

The metastable forms have different shelf lives, solubilities and bioavailabilities and due to its metastability they have the tendency to change into different forms having different properties. **For a pharmaceutical product it is important to have always the same constant properties. Only the stable form according to the present invention can ensure these constant properties.**

MYL_SOR00011392 (emphasis added).

Plaintiffs also wrote:

Since pharmaceutical compositions shall have the same reliable form for the active ingredient having the same reliable and constant properties, there is the need to use the stable polymorph.

MYL_SOR00011393.

[REDACTED]

[REDACTED]

3. A POSA Would Have Had an Expected Sorafenib Tosylate to Exhibit Polymorphism

A POSA would have expected that sorafenib tosylate would have exhibited polymorphism and would have had a reasonable expectation of success in identifying the most stable polymorph.

A very large fraction of pharmaceutical compounds demonstrate polymorphism. *See* Halebian and W. C. McCrone, “Pharmaceutical Applications of Polymorphism”, *J. Pharm. Sci.*, 58, 911-29 (1969) at 912: “The scientific literature also included numerous indications of [polymorphism’s] importance in pharmaceuticals. . . . It is now apparent that most, if not all, compounds and elements show a variety of different crystal forms.” As one of the inventors, Dr. Grunenberg has written, “Polymorphism occurs frequently in organic compounds. It has been shown that about 80% of drug substances are polymorphic.” Grunenberg, A. et al. “Theoretical derivation and practical application of energy/temperature diagrams as an instrument of preformulation studies of polymorphic drug substance,” *International Journal of Pharmaceutics*, 129 147-158 (1996) (citing Grunenberg, A., Thermische Methoden,

Thermoanalyse, In Apothekammer Nordrhein (Ed.), Regelweiterbildungsseminat Pharmazeutische Analytik, Bonn, 1992, pp. 18.).

Walter McCrone states, “It is at least this author’s opinion that every compound has different polymorphic forms and that, in general, the number of forms known for a given compound is proportional to the time and money spent in research on that compound.” W. C. McCrone, “Polymorphism” Chapter 8 in *Physics and Chemistry of the Organic Solid State*, Interscience Publishers, New York, NY (1965) at 727.

Numerous authors have either cited this statement by McCrone or have quoted him directly. In his 1987 chapter on conformational polymorphism Bernstein quotes McCrone directly, prefacing the quote by stating:

Because of its industrial importance, examples of polymorphism and techniques for investigating and utilizing it come from those areas of chemical research where full characterization of a material is crucial in determining its ultimate use, *e.g.* in pharmaceutical, dyes, and explosives. Various aspects of the subject have been treated in books and a number of reviews. The ubiquity of the phenomenon is still not generally recognized, although over twenty years ago McCrone suggested that virtually “every compound has different [sic] polymorphic forms...the number of forms for a given compound is proportional to the time and energy spent in research on that compound.”

See J. A. Bernstein, “Conformational Polymorphism,” in *Organic Solid State Chemistry*, G. R. Desiraju, ed., Elsevier, Amsterdam, 471-518 (1987) at p. 472 (“Bernstein (1987)”).

Bernstein quotes this same passage in the introduction to his 2002 book entitled “Polymorphism in Molecular Crystals” (J. A. Bernstein, Oxford University Press, Oxford, 2002, p. 8). Clearly, already by 1987, Bernstein recognized the industrial importance and “ubiquity” of polymorphism. By 2002, when his book on polymorphism was published, the importance and ubiquity of polymorphism were even more established and widely recognized in the field of pharmaceutical chemistry.

Bernstein’s sentiments are echoed by numerous authors, including Guillory and Caira. Guillory, while citing the 1965 McCrone article, quotes an equivalent statement from a 1957 publication by McCrone: “Those who study polymorphism are rapidly reaching the conclusion

that all compounds, organic and inorganic, can crystallize in different forms or polymorphs. In fact, the more diligently any system is studied, the larger the number of polymorphs studied.”

Guillory (1999) at 185. Guillory prefaces this quote with a provocative question:

One question that is likely to arise during the registration process is “What assurance can be provided that no other crystalline forms of this compound exist?” It is incumbent on the manufacturer of a new drug substance to show that due diligence has been employed to isolate and characterize the various solid-state forms of a new chemical entity. This may seem to be a daunting task, particularly in light of the widely quoted statement by Walter C. McCrone [2] that ...

Guillory (1999) at 185.

Caira (Mino R. Caira, “Crystalline Polymorphism of Organic Compounds,” *Top. Curr. Chem.*, E. Weber, Ed., **198**, 163-208 (1998) at p. 166) (“Caira (1998)”) paraphrases McCrone in a way that makes it clear that the *absence* of polymorphism is unexpected and difficult to demonstrate:

Demonstrating the absence of a tendency to polymorphism is not easy; most substances when investigated for a sufficiently long time will reveal more than one polymorph [42].

Therefore, it would have been reasonable to expect a given compound to follow this general rule, including sorafenib tosylate.

In 1990, Borka and Haleblan had published an extensive list of over 470 pharmaceutically important compounds that exhibited polymorphism. See L. Borka and J. K. Haleblan, “Crystal Polymorphism of Pharmaceuticals,” *Acta Pharm. Jugosl.* **40**, 71-94 (1990). In Chapter 7 of his book, *Polymorphism in Molecular Crystals*, Bernstein cites this paper as well as other large compilations of pharmaceutical crystal forms, including that of over 559 crystal forms reported by Griesser and Burger in 1999. Clearly, by 2002, when this book was published, those in the pharmaceutical field were well aware of the prevalence of polymorphism. Raw also teaches that identification of polymorphs is important in the pharmaceutical industry:

Unexpected appearance or disappearance of a polymorphic form may lead to serious pharmaceutical consequences, which may result in product development

delay and commercial production... As a result, pharmaceutical solid polymorphism has received much scrutiny throughout various stages of drug development, manufacturing, and regulation. For these reasons, it is essential that during drug product development and ANDA regulatory review, close attention be paid to pharmaceutical solid polymorphism.

Raw, *et al.*, “Regulatory Considerations of Pharmaceutical Solid Polymorphism in Abbreviated New Drug Applications,” *Adv. Drug. Deliv. Rev.*, **56**, 397-414 (2004).

Giron states that “Investigating the polymorphic behavior of drugs and excipients is an important part of preformulation work.” Giron (1995) also provides an extensive list of polymorphism and pseudo-polymorphism found in the literature. Giron, D. “Thermal analysis and calorimetric methods in the characterization of polymorphs and solvates.” *Thermochimica Acta* 248 1-59 (1995).

Given that many compounds commonly exhibit polymorphism, the skilled artisan would have been motivated to determine whether sorafenib tosylate can exist in multiple polymorphic states in order to exploit potentially favorable properties of one polymorph versus others, and would not have found it unexpected that sorafenib tosylate does exhibit polymorphism.

4. A POSA Would Have Been Motivated to Search for Polymorphs

“Guideline for Submitting Supporting Documentation in Drug Applications for the Manufacture of Drug Substances,” was published by Center for Drug Evaluation and Research (“CDER”), Food and Drug Administration, Department of Health and Human Services, in February 1987 (“FDA Guideline 1987”). The purpose of FDA Guideline 1987 is to provide applicants with acceptable procedures for complying with regulations regarding the production of new drug substances, specifically, drug substances manufactured by chemical synthesis. *See* FDA Guideline 1987 at 1. FDA Guideline 1987 teaches that the quality and purity of the drug substance cannot be assured solely by end-of-the-line testing, but depends on proper control of the manufacturing and synthetic process as well. *See id.* at 2. FDA Guideline 1987 further

teaches that a particular synthetic pathway will typically be uniquely associated with a set of impurities. *See id.* at 4. As set forth in the FDA Guideline 1987, FDA’s “regulations [for the manufacture of drug substances] require specifications and analytical methods ... to help assure that the proper identity, strength, quality, and purity of the drug substance have been attained and are consistent from batch to batch.” *Id.* at 25. With respect to impurities, FDA Guideline 1987 states that “[i]mpurities should not only be detected and quantitated, but should also be identified and characterized when this is possible with reasonable effort” and that “[a]ll major impurities should be individually limited.” *Id.* at 26-27.

a. Regulatory and Industry Realities

Because sorafenib tosylate was a drug candidate, a POSA would have been motivated by regulatory requirements in the United States and other countries, and the realities of pharmaceutical development to attempt to identify the most stable polymorph. *See* FDA Guideline 1987. In fact, because Bayer was already seeking regulatory approval in the United States, a POSA would have assumed that Bayer had already conducted a polymorph study, had already identified the most stable form and likely selected it for use in its product. [REDACTED]

Different forms of molecular solids, including crystalline polymorphs, crystalline solvates, and amorphous materials, display unique properties, many of which could affect the compound’s performance as a pharmaceutical. For example, forms may vary in terms of chemical properties such as solubility, dissolution rate, and bioavailability, as well as bulk properties, such as chemical stability, ease of filtering and drying, and flowability. *See* Threlfall (1995) at p. 2436. For example, polymorphs of the diabetes drug chlorpropamide have very different dissolution profiles and crushing strength, properties that affect both the administration and manufacture of this and other pharmaceuticals. *See* Byrn (1999) at 178, 274. Thus, the discovery or preparation of a polymorph or new polymorphs of a known compound is an important consideration for drug development. The strong motivation for drug

companies to discover polymorphs has been recognized in the literature. *See, e.g.*, Bernstein (2002), pp. 27, 255, 297–298; *see also* Guillory, (1999) at pp. 184-185.

Beginning in 1987, the FDA’s Guidelines For Submitting Supporting Documentation In Drug Applications For The Manufacture Of Drug Substances required polymorph screening and identification for solid dosage forms or suspension drug products. In particular, the Guidelines state:

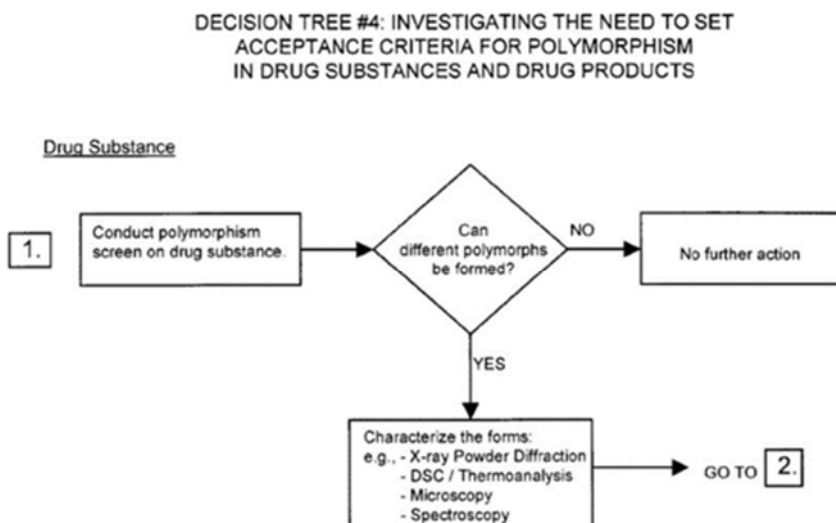
A person of ordinary skill in the art would understand that FDA’s Guidelines: regulations require, where appropriate, specifications characterizing the drug substance so as to assure the bioavailability of the drug product (*See* 21 CFR 314.50(3)(ii), and 320.52(e) [4-1–85 edition]). Certain solid-state properties of the drug substance (*e.g.* polymorphic form or amorphism, solvation or hydration, various types of inclusion complexes, and particle size or surface area) may profoundly affect dissolution and bioavailability from solid dosage forms or suspension drug products.

FDA Guideline 1987 at 31. The FDA goes on to instruct that “[a]ppropriate analytical procedures should be used to determine whether (or not) polymorphism occurs.” *Id.* at 34. The FDA required drug products to be designed to guarantee that the solid-state form would not change. In particular, FDA states that information should be provided to ensure that:

- (a) a change in solid-state form does not occur when the drug substance is manufactured and stored according to the NDA directions; or]
- (b) different forms occur but do not result in a bioavailability problem; or
- (c) polymorphism, solvation, or particle size has an important effect on bioavailability.

FDA Guidelines 1987 at 33. In addition, the FDA guidance from December 2000 explained that “[d]ifferences in these [polymorphic] forms could, in some cases, affect the quality or performance of the new drug products.” *See* FDA Guidance on Q6A Specification, 65 Federal Register 83041, 83046 (2000); *see also* ICH Harmonised Tripartite Guideline, Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances Q6A (1999) at p.8. These guidelines mention drug product stability and

bioavailability as areas where different polymorphic forms could cause different results. *See* FDA Guidance on Q6A Specification (2000) at 83046; ICH Guideline Q6A (1999) at p.8.



The FDA Q6A Specification specifically recommends that applicants conduct a polymorphic screen as the first step in investigating the need to set acceptance criteria for polymorphism in drug substances. *See* FDA Guidance on Q6A Specification (2000) at 83046, 83055; ICH Guideline Q6A (1999) at pp. 8-9, 24.

Caira notes the regulatory requirement of pharmaceutical manufacturers to provide evidence for the occurrence or absence of polymorphism in a given product. Caira states:

Already, legislation requiring drug manufacturers to provide information relating to the occurrence (or apparent absence) of polymorphism in their products has been introduced [41]. Demonstrating the absence of a tendency to polymorphism is not easy; most substances when investigated for a sufficiently long time will reveal more than one polymorph [42].

Caira (1998) at 166. Caira also states: “A recent analytical study stresses the growing need, prompted partly by legislative requirements, to differentiate polymorphs and to quantify polymorphic mixtures in pharmaceutical production [126].” Caira at 189.

Threlfall echoes these sentiments:

Much of the literature on polymorphism of organic compounds relates to pharmaceutical products. The incentive for this interest in polymorphism began

with the need to satisfy regulatory authorities in various countries as to the bioavailability of formulations of new chemical entities.

Terence L. Threlfall, *Analysis of Organic Polymorphs*, 120 ANALYST 2435, 2436 (1995)

(“Threlfall (1995)”). Byrn notes that “[i]nterest in the subject of pharmaceutical solids stems in part from the Food and Drug Administration’s (FDA’s) drug substance guideline that states ‘appropriate’ analytical procedures should be used to detect polymorphic, hydrated, or amorphous forms of the drug substance. These guidelines suggest the importance of controlling the crystal form of the drug substance.” Byrn, *Pharm. Res.*, 12, 945-954 (1995) at 945.

Vippagunta notes that:

Because different crystalline polymorphs and solvates differ in crystal packing, and/or molecular conformation as well as in lattice energy and entropy, there are usually significant differences in their physical properties, such as density, hardness, tabletability, refractive index, melting point, enthalpy of fusion, vapor pressure, solubility, dissolution rate, other thermodynamic and kinetic properties and even color [12]. Differences in physical properties of various solid forms have an important effect on the processing of drug substances into drug products [13], while differences in solubility may have implications on the absorption of the active drug from its dosage form [14], by affecting the dissolution rate and possibly the mass transport of the molecules. These concerns have led to an increased regulatory interest in understanding the solid-state properties and behavior of drug substances. For approval of a new drug, the drug substance guideline of the US Food and Drug Administration (FDA) states that “appropriate” analytical procedures need to be used to detect polymorphs, hydrates and amorphous forms of the drug substance and also stresses the importance of controlling the crystal form of the drug substance during the various stages of product development [11]. It is very important to control the crystal form of the drug during the various stages of drug development, because any phase change due to polymorph interconversions, desolvation of solvates, formation of hydrates and change in the degree of crystallinity can alter the bioavailability of the drug. When going through a phase transition, a solid drug may undergo a change in its thermodynamic properties, with consequent changes in its dissolution and transport characteristics [15].

Sudha R. Vippagunta, Harry G. Brittain, and David J. W. Grant, “Crystalline Solids,” *Adv. Drug Deliv. Revs.*, 48, 3-26 (2001)) at pp. 4-5.

Further, Beckmann wrote in 2000:

As concerns the pharmaceutical industry, it has been shown that more than half of the drug substances described in monographs crystallise in more than one solid state form, being it either polymorphs, solvates, or both.¹ The solid state form of a drug substance can influence a variety of properties, namely the solubility and rate of dissolution or the chemical stability or stability against excipients. Thus, the regulatory bodies require an exhaustive search for polymorphic forms of a drug substance

Beckmann, W. "Seeding the Desired Polymorph: Background, Possibilities, Limitations, and Case Studies," *Organic Process Research & Development* 4, 372–383 (2000).

b. Need to Understand the Energy Landscape

A POSA also would have been motivated to search for the most stable polymorph in general in order to understand the energy landscape of the solid forms of the compound. *See, e.g.* Grunenberg, A. et al. "Theoretical derivation and practical application of energy/temperature diagrams as an instrument of preformulation studies of polymorphic drug substance," *International Journal of Pharmaceutics*, 129 147-158 (1996).

In his 2002 book, "Polymorphism in Molecular Crystals," Bernstein highlights the importance of screening a compound for polymorphic behavior and the necessity of understanding the energy landscape for both the stable and metastable forms that one is able to generate. Bernstein (2002) at 252-253. This alone would provide more than enough motivation for one skilled in the art to initiate a solvent screen and other methods designed to find as many polymorphs of sorafenib tosylate as possible.

The lower solubility of stable forms may limit their pharmacological utility (*e.g.* ritonavir (Chemburkar *et al.* 2000; Bauer *et al.* 2001)), so that it may be advantageous to selectively obtain and maintain a metastable form in a formulation (*e.g.* Shah *et al.* 1999). In such cases, crystallization strategies may be designed on the basis of the principles derived from the energy-temperature or pressure-temperature diagrams (Toscani 1998), as described in Chapter 3. It will be recalled that even if qualitative in many aspects, such diagrams serve to summarize a great deal of information in a very compact manner. For instance, characterization of the two polymorphs of taltireline, a central nervous system activating agent, indicated that they were enantiotropic, but the α form, metastable at its crystallization temperature of 10° C, was preferred for formulation. Critical evaluation of the crystallization parameters isolated the factors that led to conversion of the stable form, and these were controlled to prevent conversion

(Maruyama *et al.* 1999). For a two-component system generation of the phase diagram can also prove very useful in developing strategies for obtaining a number of crystal modifications, including a metastable one (Henck *et al.* 2001).

Together with knowledge of the phase diagram an increasing variety of techniques have been designed and employed to generate metastable modifications. Seeding of course, is one of those strategies, and Beckmann *et al.* (1998) developed a seeding strategy for a batch cooling crystallization to obtain quantitatively and reproducibly a metastable form of abecarnil, regardless of the purity of the material. In another approach, after thorough characterization of three polymorphic modifications by a variety of analytical methods, a desired metastable form of (R, S)-proxiphylline was crystallized in gram quantities from the supercooled melt, and proved to have considerable kinetic stability under dry atmospheric conditions (Griesser *et al.* 2000). A variation on that same theme was the successful high-temperature crystallization from the amorphous material of the metastable a form of indomethacin, whereas the low temperature crystallization yielded the stable γ form (Andronis and Zografi 2000).

One traditional strategy for screening a compound for polymorphic behaviour involves the trial of a variety of solvents and solvent mixtures. Our understanding of the role and choice of solvent has improved considerably and this information, combined with a knowledge of zones of stability can aid in determining crystallization conditions for obtaining metastable form (Threlfall 2000). In addition, there has also been considerable progress in understanding and utilizing the interactions of solvent with the growing crystal (Weissbuch *et al.* 1991; Lahav and Leiserowitz structure determinations of polymorphs with crystal morphological data (*i.e.* crystal habit, and the orientation of molecules projecting from the particular faces exposed) and with known intermolecular interactions between solute molecules and solvent functional groups allows the rational choice of solvent to select a particular polymorphic form (Weissbuch *et al.* 1995). An analysis of this nature was carried out and experimentally confirmed by Blagden *et al.* (1998a, b) for polymorphic modification of sulphathiazole.

This is clearly an area where the combination of thermodynamic, kinetic and structural information potentially can lead to successful strategies for controlling the polymorphic form obtained, in specific instances a metastable form, and as the means for obtaining these data become more sophisticated the approaches described here are sure to be developed and expanded (*See also* Section 3.7).

Bernstein (2002) at 252-253 (emphasis added).

Giron (2004) also states:

Precise knowledge of thermodynamic stability and relationships between different solid phases is a pre-requisite for the manufacture of robust drug substance and drug products. It is also necessary to know the equilibration curves between the solid forms under the influence of the parameters humidity, temperature and

pressure in order to predict changes for storage, stability, compatibility and pharmaceutical processes. The major hurdle for the pharmaceutical industry is to have to recall medicines because of polymorphism problems as it was the case for Ritonavir.

Giron (2004) at 710.

c. A POSA Would Have Been Specifically Motivated to Use Thermal Evaluation Techniques

Thermal techniques including hot stage or thermal microscopy, DSC, and TGA have been employed for decades in the pharmaceutical industry to assess transitions between crystal forms. Byrn 1999 at 279; Caira at 178; Halebian at p. 918; Threlfall at 2439 and 2446.

Byrn provides the following flowchart/decision tree, which specifically identifies DSC and other thermoanalytical methods as part of the standard process of polymorph identification.

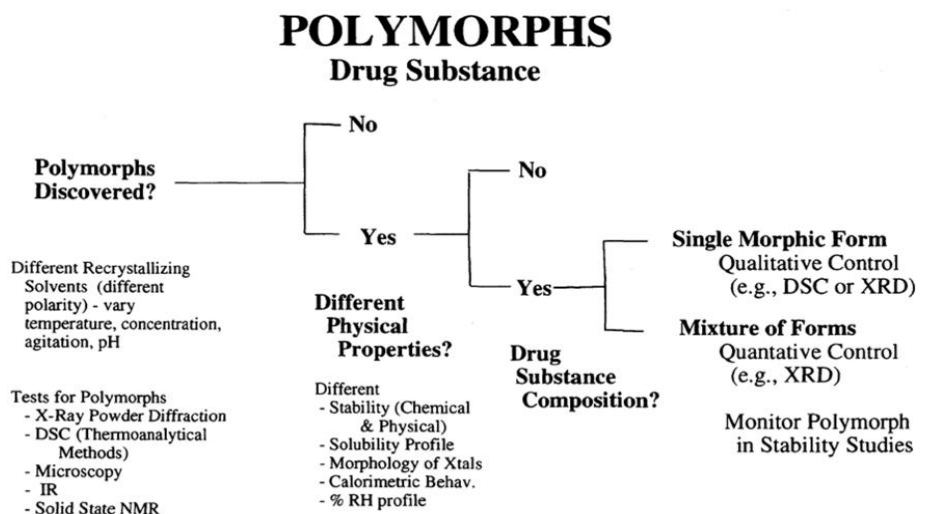


Figure 1. Flow chart/decision tree for polymorphs.
HYDRATES (SOLVATES)
Drug Substance and Solvent

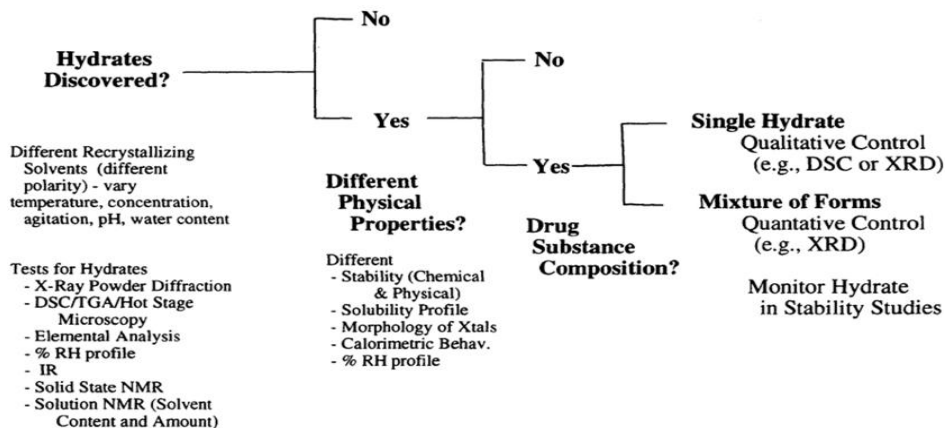


Figure 6. Flow chart for solvates or hydrates.

Based on the knowledge of a POSA, as exemplified in the literature references discussed above, it would have been obvious to a POSA to use melting point, hot-stage microscopy, DSC, or TGA to assess the relative thermal stability of any crystal form that he or she prepared. This would have inevitably produced Polymorph I.

i. Melting point

One method of characterizing crystal forms is by taking a melting point. It is often possible to distinguish two polymorphic forms by their melting points, especially when the melting points are well separated. *See, e.g.* Giron (2004).

ii. Hot-Stage Microscopy

Hot-stage microscopy has been employed for decades in the pharmaceutical industry to assess transitions between crystal forms. In this method, the sample is heated gradually on a microscope stage while events are recorded visually or with either photographs or videos. This is a convenient technique that allows a scientist to visually observe and record phase changes as a function of temperature. Hot-stage microscopy is often used in conjunction with differential scanning calorimetry (“DSC”).

Threlfall recognizes that hot stage microscopy is a technique for generating polymorphs. In particular, he states: “hot-stage microscopy has been often so used and remains the outstanding method for the examination and generation of polymorphs.” Threlfall (1996) at 2439. He further states:

A preliminary examination under a binocular microscope will enable the overall characteristics of the sample to be ascertained. Temperature cycling and melt and solvent recrystallization experiments with a polarizing microscope equipped with a hot-stage will allow the identification of transition points, the distinguishing of monotropic and enantiotropic relationships, estimation of the tendency of melts and individual phases to supercool, ***the generation of stable and unstable polymorphs*** and the recording of their optical properties. The identification of solvates and the observation of sublimates and of any tendency to decompose are added information. This can be carried out with minute amounts of material. The field has been excellently and comprehensively reviewed in the past, and for that reason only the developments since then will be considered in detail here.

Threlfall at 2439 (emphasis added); *See also* Byrn (1999) at 279; Caira (1998) at 178; Haleblan (1969) at 918. Thus, hot stage microscopy is an important tool for investigating polymorphism of crystalline solids.

iii. Differential Scanning Calorimetry (“DSC”)

Differential Scanning Calorimetry (“DSC”) is a type of test that can be used to measure the melting point of a material. DSC uses the thermal characteristics of different phase transitions to distinguish between different materials. In DSC, one applies enough thermal energy (or power) to the sample and a reference to keep them at the same temperature while warming or cooling. The DSC data is in the form of a curve showing the heat flow as a function of sample temperature. The direction of the peak (which is either endothermic or exothermic) helps to identify the type of transformation taking place.

The DSC trace complements the melting point by providing detailed information about the melting transition, including the enthalpy of fusion (i.e., the heat energy that must be added to melt a specific amount of the substance), which is a characteristic property of each crystalline form. The DSC can provide diagnostic information related to pre-melting behavior, phase transitions, decomplexation of bound solvent, and chemical decomposition.

In particular, DSC is used throughout the pharmaceutical industry to identify new crystalline forms of drug substances. Both desolvation and solid-solid phase transformations give rise to signals in the DSC trace and would prompt further investigation of the crystal forms generated by these thermal processes. *See, e.g.,* Shami, E. *et al* “Preformulation” in *Theory and Practice of Industrial Pharmacy* (1976) at 4 (worksheet for summarizing data, and noting melting point and DSC in particular).

iv. Thermogravimetric Analysis (“TGA”)

In a thermogravimetric analysis (or thermogravimetry), the mass of a compound is monitored as a function of temperature. Typically, a known amount of sample is heated at a constant rate, and the loss of mass due to decomposition or evaporation is recorded as a

function of time while an inert gas is flowed past the sample. Both the mass of the sample and the first derivative (mass loss per temperature unit) are plotted as a function of temperature.

v. Drying

In any organic synthesis that generates a final product, the sample is dried so that the yield can be reported and the sample can be analyzed. New compounds in particular are subjected to elemental analysis, which requires a dried sample (i.e., with no solvent, if possible). Wiberg describes the necessity for engaging in the drying process. He states: “After recrystallization it is usually necessary to dry the material.” Wiberg (1960) at pp. 109-110. Thus a POSA would have dried any sample of sorafenib tosylate produced, which would have inherently produce Polymorph I.

d. A POSA Would Have Been Specifically Motivated to Conducted a Polymorph Screen

As noted in Plaintiffs’ statements to the European Patent Office, POSA would have been motivated to seek the most stable polymorphic form of sorafenib tosylate because that form would be unlikely to convert to a different polymorphic form that could negatively impact a drug product’s quality or performance.

There are numerous references that demonstrate motivation and knowledge. For example, in his chapter entitled, “Preformulation,” Fiese, *et al.*, states:

During preformulation, it is important to identify the polymorph that is stable at room temperature and to determine whether polymorphic transitions are possible within the temperature range used for stability studies and during processing (drying, milling, etc.).

Eugene F. Fiese, *et al.*, Chapter 8 in *The Theory and Practice of Industrial Pharmacy*, Lachman, *et al.*, Eds., Lea & Febiger, 171-96 (1986) at pp. 180-81.

Caira explains that when developing a new drug product, “[s]ystematic investigation of a compound to determine whether it is prone to polymorphism . . . is routine practice in pharmaceutical pre-formulation studies. Identification of the different polymorphic forms of a drug substance . . . [is] essential for ensuring drug preparations with reproducible behaviour.”

Caira at 165-66.

Similarly, Guillory explains that “[i]t is incumbent on the manufacturer of a new drug substance to show that due diligence has been employed to isolate and characterize the various solid-state forms of a new chemical entity.” Guillory at 185.

Threlfall further explains:

As formulations have become more sophisticated and as the tolerances on products have become tighter, the need to identify polymorphic behaviour at an early stage of development has become important in the pharmaceutical industry as a means of ensuring reliable and robust processes and conformity with good manufacturing practice. The aim is to avoid, *inter alia*, tableting problems and subsequent tablet failure, crystal growth in suspension and resultant caking, precipitation from solutions and problems with suppositories, as well as chemical production problems such as filtrability and to ensure analytical reproducibility.

Threlfall (1995) at 2436.

Byrn provides further motivation to conduct studies of polymorphism of pharmaceuticals in section 13.3 of his book at 266-278. Byrn (1999). Here, he cautions the reader that changes in polymorphic form might affect the solubility and bioavailability of the pharmaceutical:

13.3 POLYMORPHIC TRANSFORMATIONS OF PHARMACEUTICALS

In this section, studies of drugs that undergo polymorphic transformation are reviewed and discussed. This is an important area of research because of its implications in the physical stability of drug dosage forms. As mentioned earlier, different polymorphs possess different physical properties-solubility and bioavailability being the most important. In addition, keep in mind that changing the temperature or pressure during a manufacturing operation, such as tableting, could induce a polymorphic transformation.

Byrn (1999) at 266. *See also* Shami, E. *et al* “Preformulation” in Theory and Practice of Industrial Pharmacy (1976) at 3 (“Investigating the polymorphic properties is important, since polymorphic forms in many cases exhibit differences in biological availability.”).

The vast majority of drugs use the most stable form of the drug as the commercial active pharmaceutical ingredient. In the context of pharmaceuticals, the most stable

polymorphic form is a preferred form, because, for example, it can extend the shelf life of the drug. Haleblan (1969) at 912-13; MYL_SOR0012929.

The most stable form is most frequently chosen for commercial development because of risk of conversion.

The goal in any industrial pharmaceutical organization is to have the thermodynamically preferred polymorph or solvate present in the first scaled-up batch of drug substance. If this situation is achieved, then all toxicology, pharmacokinetic, and clinical studies will be conducted with the crystalline form that is likely to be the commercial form of the drug substance. This will eliminate expensive retesting should a more stable but previously unknown polymorph appear. Prudent drug development programs will identify the preferred crystalline form early in development, with a polymorph/salt group working in close conjunction with process chemists to make the thermodynamically preferred polymorphic form the initial kilogram-scale batch. They will also identify and define the physicochemical boundaries of that polymorph.

Harry G. Brittain and Eugene F. Fieser, “Effects of Pharmaceutical Processing on Drug Polymorphs and Solvates,” in *Polymorphism in Pharmaceutical Solids*, Harry G. Brittain, Ed., Marcel Dekker, Inc., New York, NY, 331-361 (1999) at 358.

Accordingly, the goal of understanding the thermodynamic relations between the different crystal forms, and in particular the relation of other forms to the most thermodynamically stable polymorphic form of a drug substance, is a significant consideration during drug product development.

Caira cites safety reasons for the control of crystal form used in pharmaceuticals: Solubility and dissolution rate analyses are of vital importance for polymorphs and pseudopolymorphs of pharmaceutical relevance. For a given drug, metastable polymorphs tend to have higher solubilities and faster dissolution rates than the stable polymorph. When metastable forms are employed in solid dosage forms (tablets, capsules), they generally yield higher and earlier blood serum levels [25]. Thus, for potent drugs with a narrow therapeutic index (*e.g.* the cardiotonic digoxin), inadvertent use of a metastable polymorph in a tablet could result in patient death from overdose. In vitro dissolution testing is therefore carried out routinely as part of the quality control of manufactured tablets and capsules.

Caira (1998) at 165-66.

Guillory urges early assessment of the relative stabilities of different crystal forms because of the possibility of conversion from a metastable form to a more stable one:

It is essential to ascertain whether the crystalline material that results from a synthetic procedure is thermodynamically stable before conducting pivotal trials, since a more stable form may be obtained subsequently, and it may be impossible to produce the metastable form in future syntheses. Conversion from one polymorph to another can occur during processing or upon storage.

Guillory (1999) at 184.

Repeating these same principles, Yu explains that:

The widespread existence of polymorphic drugs underscores the importance of an efficient and consistent characterization strategy. The potential impact of changing crystal forms during late-stage development in terms of cost and product delay justifies the systematic and early characterization of polymorphism.

See L. Yu, “Physical characterization of polymorphic drugs: an integrated characterization strategy,” PSTT, 1, 118-27 (1998) at 125-26 (“Yu (1998)”).

It was known in the art as of the priority date that polymorph screening was necessary to ensure consistent, bioavailable, and stable drug product, as Plaintiffs themselves admitted. It was also known that the consequences of not investigating the relative stabilities of different crystal forms and their ease of conversion could be devastating, both for the manufacturer, and, in some cases, for public health. In 1996, Abbott Laboratories began to market a semi-solid capsule of ritonavir (NorvirTM), which was an important protease inhibitor used in the fight against HIV/AIDS. Because of its low bioavailability and low solubility, ritonavir was formulated in an ethanol/water solution. In 1998, after 240 lots had been produced without any solubility problems, certain capsules began to fail the dissolution tests as a new, more stable polymorph emerged. S. Chemburkar, “Dealing with the Impact of Ritonavir Polymorphs on the Late Stages of Bulk Drug Process Development,” *Organic Process Research & Dev.*, 4, 413-417 (2000) at 413. Soon thereafter, it was no longer possible to generate the original metastable form as “seeds” of the more stable form infiltrated laboratories and manufacturing plants. *Id.* The sudden appearance of this stable form of ritonavir and the great difficulty in manufacturing the metastable form required Abbott to remove ritonavir from the market for over a year as it searched for a new formulation. *Id.*; see also Bauer, J. et al, “Ritonavir: An

Extraordinary Example of Conformational Polymorphism,” *Pharmaceutical Research*, 18, 6 859-866 (2001).

The prior art experience with ritonavir presents a cautionary tale that the pharmaceutical industry has taken to heart. Chemburkar (from Abbott) writes: “It is highly advisable to put enough resources to carry on exhaustive research to identify the most stable and all possible polymorphs.” Chemburkar at 417. *See also* Bauer, J. et al, “Ritonavir: An Extraordinary Example of Conformational Polymorphism,” *Pharmaceutical Research*, 18, 6 859-866 (2001) at 859 (noting that because ritonavir was in ethanol/water solution “no crystal form control was required” under the then-operative ICH guidelines).

Thus a POSA as of the priority date would have been keenly aware of the necessity of performing a polymorph screen and identifying the most thermodynamically stable polymorph of a drug substance such as sorafenib tosylate.

A POSA would therefore have been specifically motivated to attempt to identify the most stable polymorph of sorafenib tosylate.

e. Solution-Mediated Transformations and “Slurrying”

As noted above, a POSA would have been motivated to find the most stable form of sorafenib tosylate for pharmaceutical development.

In practice, the simplest and most typical way of searching for the most stable crystal form involves a “slurry conversion,” in which the different crystal forms of a particular compound are rapidly stirred over a period of hours or days in the presence of solvent sufficient to dissolve only a small amount of the substance in question. Haleblan (1969) at 922.

Because the most thermodynamically stable polymorph generally has the lowest solubility, this process, which typically involves dynamic dissolution and recrystallization, can be used to convert less stable polymorphs into the most thermodynamically stable polymorph.

Threlfall (1995) at 2449 (“The solubility also has an important thermodynamic feature: it is inversely related to the stability of the polymorph such that the most stable polymorph is always the least soluble at a given temperature.”).

A POSA would understand that a reliable way of identifying the most stable crystal form of sorafenib tosylate would be to slurry any of the solid forms that might be generated in several different solvents and to compare the results of these slurries by using powder X-ray diffraction. *See, e.g.* Gu, C-H et al. “Polymorphic Screening: Influence of Solvents on the Rate of Solvent-Mediate Polymorphic Transformation”, *Journal of Pharmaceutical Sciences* 90, 11 1878-1890 (2001). PRACTICAL PROCESS RESEARCH & DEVELOPMENT, authored by Neal G. Anderson, was published by Academic Press in 2000 (“Anderson”). Anderson teaches the general practice in many aspects of process research and development, and particularly pharmaceutical process research and development, including process optimization, purification and control of impurities. *See* Anderson, Chapters 8 and 11. For example, Anderson teaches techniques for optimizing reactions to minimize impurities and “tools for purifying the product by column chromatography, crystallization and reslurrying.” *Id.*

Caira cites earlier literature on solvent-mediated transformations, whose driving force is the difference in solubility between different forms:

Theoretical and experimental studies of the role of solvent on polymorphic crystallization and phase transformations abound in the literature of the last few years and some pertinent examples are described here. For solvent-mediated transformations, the driving force is the difference in solubility between different polymorphs. An important earlier paper on the kinetics of such phase transformations [51] described a model featuring two kinetic processes in solid to solid phase changes via a solution phase, namely dissolution of the metastable phase and growth of the stable one.

Caira (1998) at 169.

Grant also discusses the use of solution-mediated phase transformations of metastable polymorphs to give more stable ones:

Under appropriate thermodynamic conditions discussed at the beginning of this chapter, a less stable polymorph may be converted into a more stable polymorph.

The rate of conversion to the more stable polymorph is often rapid, if mediated by the solution phase or vapor phase. In these phases the less stable polymorph (having the greater solubility or vapor pressure) dissolves or sublimates, while the more stable polymorph (having the lower solubility or vapor pressure) crystallizes out.

Grant (1999) at 26.

Rodriguez-Hornedo provides the same sentiments:

Knowledge of the propensity of a metastable solid phase to dissolve in a liquid phase from which a stable solid phase nucleates and grows is crucial in many stages of pharmaceutical development, because pharmaceutical solids are designed to be dissolved and to come in contact with solvents since the early stages of development (isolated by crystallization from solution) and during processing (wet granulation, spray-drying, freeze-drying, etc.). Given that the sudden disappearance or appearance of a crystalline modification can threaten process development, characterization of the kinetics and mechanisms of solvent-mediated transformations is of practical importance.

Naír Rodríguez-Hornedo and Denette Murphy, “Significance of Controlling Crystallization Mechanisms and Kinetics in Pharmaceutical Systems,” *J. Pharm. Sci.*, **88**, 651-660 (1999) at 657.

Guillory also explains that slurries result in the conversion from a metastable polymorph to a more stable one through a solution phase mediated transformation:

According to McCrone, in a poor solvent the rate of transformation of a metastable to a more stable polymorph is slower. Hence a metastable form once crystallized can be isolated and dried before it is converted to a more stable phase by solution phase mediated transformation.

Guillory at 193 (citing W. C. McCrone, “Polymorphism,” Chapter 8 in *Physics and Chemistry of the Organic Solid State*, Vol. II (D. Fox, M. M. Labes, and A. Weissberger, Eds.), Interscience, New York, (1965).

Kiyotaka Sato (“Polymorphic transformations in crystal growth,” *J. Phys. D: Appl. Phys.*, 26, B77-B84 (1993) writes:

The driving force of these transformations is the Gibbs energy difference between the polymorphs. Ostwald ripening is a well-known similar phenomenon. It dictates an achievement of a free energy minimum condition in a crystal-medium system consisting of a poly-disperse precipitate, governed by the difference in solubility between the poly-disperse crystal particles [21].

f. A POSA Would Have Been Motivated to Run a Standard Solvent Screen

A POSA also would have been motivated to run a standard polymorph screen using routine solvents and recrystallization conditions with a reasonable expectation of success to form crystalline solids.

In addition to the techniques discussed above, there are a number of standard techniques that scientists use to screen for polymorphs. In his book entitled, “Polymorphism in Molecular Crystals,” Bernstein emphasizes the role of solvent screens in finding new polymorphic forms:

One traditional strategy for screening a compound for polymorphic behaviour involves the trial of a variety of solvents and solvent mixtures. Our understanding of the role and choice of solvent has improved considerably and this information, combined with acknowledge of zones of stability can aid in determining crystallization conditions for obtaining metastable form (Threlfall 2000). In addition, there has also been considerable progress in understanding and utilizing the interactions of solvent with the growing crystal (Weissbuch *et al.* 1991; Lahav and Leiserowitz structure determinations of polymorphs with crystal morphological data (*i.e.* crystal habit, and the orientation of molecules projecting from the particular faces exposed) and with known intermolecular interactions between solute molecules and solvent functional groups allows the rational choice of solvent to select a particular polymorphic form (Weissbuch *et al.* 1995). An analysis of this nature was carried out and experimentally confirmed by Blagden *et al.* (1998a, b) for polymorphic modification of sulphathiazole.

Bernstein (2002) at 252.

In his chapter entitled, “Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids” (*Polymorphism in Pharmaceutical Solids*, H. G. Brittain, Ed., 183-226 (1999) at pp. 184-202), Guillory describes a screening protocol that can be used by those in the pharmaceutical industry:

In this context, it is hoped that the following information will prove useful in devising a “screening” protocol for the preparation of the various solid state forms of pharmaceuticals. While one cannot be absolutely certain that no additional forms will be identified in the future, this approach should provide some assurance that “due diligence” has been exercised to isolate and identify crystalline forms that are likely to arise during the normal course of drug development and storage.”

Guillory (1999) at 186.

C. A POSA Would Have Had a Reasonable Expectation of Success in Identifying the Most Stable Polymorphic Form of Sorafenib Tosylate.

The most stable crystalline form of a compound is usually the most readily obtainable form. It would have been routine—and obvious—for a POSA to have obtained the most thermodynamically stable polymorphic form of sorafenib tosylate. For example, a POSA would have used any of the standard techniques to take a melting point of sorafenib tosylate, or their equivalent (DSC, hot bar, TGA, etc) that would have inevitably produced Form 1.

As described above, a POSA would have, for example, slurried sorafenib tosylate in a number of solvents at ambient conditions and would have obtained Form 1 as the most stable polymorph. *See* Bernstein (2002) pp. 27, 255, 297-298.

Therefore, as discussed above, a POSA would have had good reasons to conduct polymorphic screening for sorafenib tosylate (thereby obtaining Polymorph I) and would then have ascertained Polymorph I as the most thermodynamically stable polymorphic form among those generated.

D. The Asserted Claims Would Have Been Obvious

Claims to Polymorph I are obvious because a POSA would have been motivated to run, for example, standard thermal and analytical techniques on any form of sorafenib tosylate, a routine solution-mediated transformation experiment (slurry experiment), or a solvent screen with a reasonable expectation of success to identify the most thermodynamically stable crystalline form of sorafenib tosylate. *See* Guillory (1999) at 191-192; *see also* Byrn (1999) at 274-277. Form 1 was an inevitable result of such slurry experiments.

Also explained above, it was well known in the art that characterization of polymorphs of a solid drug substance was an important aspect of drug development, and a required part of the new drug approval process. *See, e.g.*, Guillory (1999) at 184-185; Byrn (1995) at 945; ICH guidelines at 1, 8. Furthermore, it was well known in the art that the most thermodynamically stable polymorphic form of a drug substance was generally the preferred form for purposes of formulating the drug. *See, e.g.*, Chemburkar (2000) at 413-417; Byrn (1995) at 946-948; Guillory (1999) at 184-186; C. Gu, “Polymorph Screening: Influence of Solvents on the Rate of

Solvent-Mediated Polymorphic Transformation,” *J. Pharm. Sci.*, 90, 1878-1889 (2001); S. L. Morissette, “High-throughput crystallization: polymorphs, salts, co-crystals and solvates of pharmaceutical solids,” *Advanced Drug Delivery Reviews*, 56, 275-300 (2004) at 275-278, 285-291.

Having identified Form 1 as the thermodynamically stable form using routine solvent screens and slurry experiments, a POSA would have been motivated to choose Form 1 as the active pharmaceutical ingredient for development. *See* Guillory at 188-191; Byrn (1995) at 946.

1. Claims 1-4 and 27-31

Claims 1-4 and 27-31 recite sorafenib tosylate Polymorph I and with properties such as specific PXRD reflections, Raman spectroscopy maxima, IR maxima, and melting point. Each of these additional limitations are inherent properties of sorafenib tosylate Polymorph I. Because Polymorph I is obvious, these additional limitations are likewise obvious.

2. Claim 8-10

Claims 8, 9, 10 of '933 patent relate to pharmaceutical formulations comprising sorafenib tosylate Polymorph I. Noted above, it was common to select the most stable polymorph of a compound like sorafenib tosylate for use in a pharmaceutical composition. For example, as taught by Guillory, one of skill in the art would know to employ the thermodynamically stable form a compound during formulation generation. Guillory at 184; *see also* November 9, 2015 Notice Letter at 73-74.

Claim 9 depends from claim 8 and includes the further limitation of including inert, nontoxic, pharmaceutically suitable excipients in the composition. Numerous prior art references, including U.S. Patent App. Pub. No. 2003/0232765 to Carter et al. (“Carter”), disclose the use of such excipients, as described in the November 9, 2015 Notice Letter. November 9, 2015 Notice Letter at 72-73, 106; Carter at ¶ 65. Similarly, U.S. Patent App. Pub. US 2003/0207870 to Dumas et al. ('870 Publication) discloses the use of such excipients together with sorafenib.

Claim 10 depends from claim 8 and specifies that the sorafenib tosylate present in the composition be at least 90% (by weight) sorafenib tosylate Polymorph I.

BAYER_NEXAVAR_00102008.

Accordingly, claims 8-10 are invalid as obvious.

3. Claims 16-21

Claim 16 relates to administering a therapeutically effective amount of sorafenib tosylate Polymorph I. Because sorafenib tosylate was a known active pharmaceutical composition, it would have been obvious to administer an effective amount to treat some condition. *See e.g.*, Carter at ¶¶ 36, 45; *see also* '870 Publication. Combined with the reasons articulated above for claim 1, claim 16 is invalid.

Claim 17 depends from claim 16 and specifies that the disorder is abnormal angiogenesis, hyperpermeability processes, bone marrow diseases, carcinoma and carcinogenic cell growth. Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. Carter at ¶¶ 36, 45; *see also* 870 Publication. Combined with the reasons articulated above for claim 1, claim 17 is invalid as obvious.

Claim 18 depends from claim 16 and specifies that the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid, kidney, or intestine. Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. Carter at ¶¶ 36, 45; '870 Publication. Thus, claim 18 is invalid as obvious.

Claim 19 recites a method for treating a disorder, comprising administering a therapeutically effective amount of the compositions of any one of claims 8 to 15. For the same reasons articulated for claims 8 to 10 and claims 16, claim 19 is invalid as obvious.

Claim 20 depends from claim 19 and specifies that the disorder is abnormal angiogenesis, hyperpermeability processes, bone marrow diseases, carcinoma and carcinogenic cell growth. Carter teaches the treatment of various cancers, including pancreatic, lung, colon,

ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. Carter at ¶¶ 36, 45. Combined with the reasons articulated above for claim 1, 17 and 19, claim 20 is invalid as obvious.

Claim 21 depends from claim 19 and specifies that the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid, kidney, or intestine. Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. Carter at ¶¶ 36, 45. Combined with the reasons articulated above for claim 1, 17 and 19, and 20, Claim 21 is invalid as obvious.

E. Obviousness-type Double Patenting

The '933 patent also is invalid for obviousness-type double patenting over U.S. Patents No. 7,351,834 ("the '834 patent") and 8,618,141 ("the '141 patent"), both of which are commonly owned, licensed or assigned with the '933 patent and expire before it.

The '834 patent issued April 1, 2008. It expires January 12, 2020, according to the Orange Book. Each of the Asserted Claims of the '933 patent is invalid for obviousness-type double patenting over at least claim 41 of the '834 patent. Claim 41 is directed to: "A compound of claim 39 which is a tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N' - (4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea."

The '141 patent issued December 31, 2013. It expires February 11, 2023, according to the Orange Book. Each of the Asserted Claims of the '933 patent is invalid for obviousness-type double patenting over at least claim 6 of the '141 patent. Claim 6 is directed to:

A method of blocking tumor angiogenesis in a human or other mammal comprising administering to a human or other mammal with a tumor of the breast, gastrointestinal tract, kidney, ovary or cervix, an effective amount of the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea tosylate

Each of the Asserted Claims is an obvious variant of the subject matter of the claims of the '834 and '141 patents for the reasons set out above.

SECOND SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 5:

Mylan incorporates by reference the General Objections, Objections to Definitions and Instructions, and each specific objection set forth above as if fully stated herein. Mylan further incorporates by reference Defendant Mylan's Response and First Supplemental Response to Interrogatory No. 3, as if fully set forth herein. Mylan supplements its response to Interrogatory No. 3 as follows:

I. U.S. PATENT NO. 8,618,141**A. Obviousness**

Each of the Asserted Claims of the '141 patent is invalid as obvious over the prior art described above and in this section. As of the priority date of the '141 patent, a POSA would have been strongly motivated to treat kidney tumors with sorafenib tosylate and would have had a reasonable expectation of success in doing so.

Additionally, each of the Asserted Claims of the '141 patent is invalid as obvious over the '012 Publication in view of Grugel, Stefan et al., *Both v-Ha-Ras and v-Raf Stimulate Expression of the Vascular Endothelial Growth Factor in NIH 3T3 Cells*, 270 J. of Biological Chem. 43, 25915, 25918 (1995) ("Grugel"), Kieser, Arnd et al., *Mutant p53 potentiates protein kinase C induction of vascular endothelial growth factor expression*, *Oncogene* (1994) 9, 968 ("Kieser"), Ellis, Lee M. et al., *Vascular Endothelial Growth Factor in Human Colon Cancer: Biology and Therapeutic Implications*, *The Oncologist* 2000; 5 (suppl. 1):11-15 (February 2000) ("Ellis"); or Karashima, Takashi et al., *Treatment of Human Metastatic Transitional Cell Carcinoma of the Bladder in a Murine Model with the Anti-Vascular Endothelial Growth Factor Receptor Monoclonal Antibody DC101 and Paclitaxel*, *Clinical Cancer Research* Vol. 6, 2635-2643, 2635 (July 2000) ("Karashima") each or in combination with one another. By the time of the filing of the application that lead to the '141 patent, the method of treating patients with tumors by administration of sorafenib tosylate was known. '012 Publication at 2. The essential role of the ras/raf signal transduction pathway in the regulation of VEGF expression in

mouse embryo cells was also known. Grugel at 25918. As of 1994, the role of p53 in tumorigenesis and its link to expression of VEGF was also known. *See* Kieser at 968. In 1995, Grugel postulated that “Ras as well as Raf are not only involved in cell proliferation and differentiation but also in tumor progression, mediated by increased expression of the tumor angiogenesis factor VEGF.” Grugel at 25918. VEGFR-2 was known as a high affinity VEGF receptor tyrosine kinase. Ellis at 11-15. As of the priority date, VEGFR was known to regulate angiogenesis and metastasis of bladder cancer. Karashima at 2635 (July 2000). Thus, as of the priority date, a POSA would have been motivated to treat kidney tumors characterized by abnormal angiogenesis and hyperpermeability processes mediated by the VEGFR-2-pathway using a drug known to inhibit the raf kinase pathway in other solid cancers. *See* ’012 Publication at 2.

Accordingly, each of the Asserted Claims of the ’141 patent are obvious in view of the prior art discussed above.

B. Lack of Enablement and Written Description

Claims 7-9 and 11 of the ’141 patent claim a method of blocking angiogenesis in “a tumor of the kidney.” As discussed in the Response to Interrogatory No. 3 above, there are no examples, data or other information that would permit a person to practice the full scope of this claim without undue experimentation. Therefore, these claims are invalid for lack of enablement and written description under § 112(a).

II. U.S. PATENT NO. 8,877,933

A. Anticipation by Public Use

A patent is invalid as anticipated if “the invention was . . . in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.” 35 U.S.C. § 102(b); *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1343 (Fed. Cir. 2005). Each of the Asserted Claims of the ’933 patent also are invalid as anticipated

or obvious under 35 U.S.C. § 102(b) due to public use of the claimed invention in the United States before the earliest claimed priority date.

Under § 102(b), an invalidating public use occurs when, “before the critical date, the invention is in public use and ready for patenting.” *Invitrogen Corp. v. Biocrest Manufacturing L.P.*, 424 F.3d 1374, 1379 (Fed. Cir. 2005). An invalidating public use under § 102(b) “includes any use of the claimed invention by a person other than the inventor who is under no limitation, restriction or obligation of secrecy to the inventor.” *Netscape Commc'ns Corp. v. Konrad*, 295 F.3d 1315, 1320 (Fed. Cir. 2002); *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1297 (Fed. Cir. 2002). To avoid an invalidating public use, confidentiality obligations must be imposed on those that use or observe the invention. *See, e.g., Netscape*, 295 F.3d at 1323 (holding that the inventor's failure to impose confidentiality agreements on those who used the invention placed the invention in public use); *MSM Investments Co. v. Carolwood Corp.*, 70 F. Supp. 2d 1044, 1053 (N.D. Cal. 1999) (same). An invention is ready for patenting if (1) it has been reduced to practice; or (2) the inventor had prepared descriptions of the invention that were sufficiently specific to enable a person skilled in the art to practice the invention. *Pfaff v. Wells Elecs.*, 525 U.S. 55, 67-68 (1998).

The subject of the '933 patent was ready for patenting well before the priority date.

[REDACTED] These public uses in the U.S. show that the '933 patent was ready for patenting at least as early as November 9, 2000, nearly four years before the claimed priority date.

Polymorph I, the subject of the '933 patent, was used in these U.S. clinical trials.

[REDACTED]
[REDACTED]
[REDACTED] For the reasons stated in the First Supplemental Response, Polymorph I is anticipated or obviated by the drug compound called sorafenib.

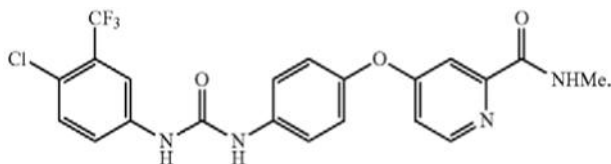
Accordingly, the Asserted Claims of the '933 patent are anticipated or obvious.

B. Obviousness-type Double Patenting

The '141 patent issued December 31, 2013. It expires February 11, 2023, according to the Orange Book. Each of the Asserted Claims of the '933 patent is invalid for obviousness-type double patenting over at least claims 6-11 of the '141 patent. The text of claim 6 is set out above.

Claim 7 is directed to:

A method of blocking tumor angiogenesis in a human or other mammal comprising administering to a human or other mammal with a tumor of the kidney an effective amount of the tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula below



Claim 8 depends on claim 7 and is directed to:

A method as in claim 7 wherein the tumor of the kidney that is treated is characterized by abnormal angiogenesis or hyperpermeability processes, which are not raf-mediated nor p38-mediated.

Claim 9 depends on claim 8 and is directed to:

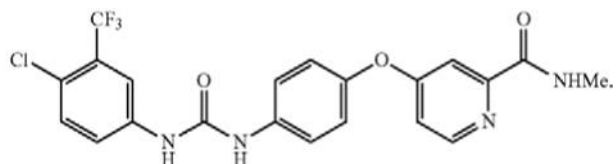
A method as in claim 8 wherein the tumor of the kidney that is treated is characterized by abnormal angiogenesis or hyperpermeability processes, which are mediated by KDR (VEGFR-2).

Claim 10 depends on claim 6 and is directed to:

The method of claim 6, wherein the effective amount of the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea tosylate is between 0.01 to 200 mg/Kg of total body weight.

Claim 11 depends on claim 7 and is directed to:

The method of claim 7, wherein the effective amount of the compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formulate below is between 0.01 to 200 mg/Kg of total body weight.



Each of the Asserted Claims of the '933 patent is an obvious variant of the subject matter of claims 6-11 of the '141 patents for essentially the reasons set out above regarding obviousness, with certain difference because of the different legal standards applied in obviousness-type double patenting. For example, in an obviousness-type double patenting analysis there is no obligation to identify reasons to start with the subject matter of the prior claim and secondary considerations are not considered.

On the facts here, in addition to the facts set out above, the Asserted Claims of the '933 patent are obvious variants of the claims of the '141 patent because, for example, the earlier-expiring claims are explicitly directed to a "method of blocking tumor angiogenesis in a human" using sorafenib tosylate. This would have specifically motivated a POSA to identify the most stable polymorph as required by FDA guidance, the other reference described above regarding obviousness.

In addition, the claims of the '141 patent specifically include within their claim scope elements of Asserted Claims 17-21 of the '933 patent, further rendering those claim obvious variants of the earlier-expiring claims.

Claims 16-21 of the '933 patent are directed to:

16. A method of treating a disorder, comprising administering to a subject in need thereof a therapeutically effective amount of [sorafenib tosylate] in the polymorph I form which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5.

17. The method of claim 16, wherein the disorder is selected from the group consisting of **abnormal angiogenesis**, hyperpermiability processes, bone marrow diseases, carcinoma and carcinogenic cell growth.

18. The method of claim 16, wherein the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid gland, kidney or intestine.

19. A method for treating a disorder, comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of any one of claims 8 to 15.

20. The method of claim 19, wherein the disorder is selected from the group consisting of **abnormal angiogenesis**, hyperpermiability processes, bone marrow diseases, **carcinoma and carcinogenic cell growth**.

21. The method of claim 19, wherein the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid gland, **kidney** or intestine.

For example, claims 17 and 20 of the '933 patent are obvious variants of claims 8 and 9 of the '141 patent because claims to Polymorph I are obvious variants of the earlier claims and because the earlier claims further define elements of claims 16, 17, 19, and 20 (*e.g.*, disorders including abnormal angiogenesis and hyperpermiability processes). Similarly, claims 18 and 21 of the '933 patent are directed to methods of treating, *e.g.*, carcinoma of the kidney, which is an element of claim 7 of the '141 patent and its dependent claims.

In addition, a POSA would understand that the sorafenib tosylate would have to be administered to a human as “pharmaceutical composition” with “one or more inert, nontoxic, pharmaceutically suitable excipients” as required by claims 8-9 of the ’933 patent in order to practice the methods of any of the claims of the ’141 patent. A POSA would prefer that the composition include, ideally, only the most stable polymorph (*i.e.*, Polymorph I) to preclude changes in the drug product over time. For example, as explained above, one of skill in the art would employ the most thermodynamically stable form a compound during formulation generation. *See, e.g.*, Guillory at 184-186; Chemburkar (2000) at 413-417; Byrn (1995) at 946-948. This is confirmed by Plaintiffs: “It is very important for a pharmaceutical product to have always the same constant properties... For a pharmaceutical product it is important to have always the same constant properties. Only the stable form according to the present invention can ensure these constant properties.” MYL_SOR00011392. Thus it would have been obvious for a pharmaceutical composition to contain more than 90% of Polymorph I. A POSA would prefer that the composition include, ideally, only the most stable polymorph (*i.e.*, Polymorph I) to preclude changes in the drug product over time.

INTERROGATORY NO. 4:

Other than as set forth in your responses to Interrogatory Nos. 1-3, is there any other basis on which you contend that the Court should not find that the manufacture, use, offer for sale, sale, or importation of Mylan’s ANDA Product would infringe at least one valid and enforceable claim of the patents-in-suit or that you are not liable for inducing the infringement of one or more claims of the patents-in-suit? If your answer is anything other than an unequivocal “no,” state all bases for your contention and identify for each challenged claim all facts, documents, and circumstances on which you rely for your contention.

RESPONSE TO INTERROGATORY NO. 6:

Mylan incorporates the General Objections set forth above. Mylan objects to this interrogatory as overly broad, unduly burdensome, and oppressive to the extent it seeks information that is irrelevant to the claims and defenses at issue in this case and is not

proportional to the needs of the case. For example, Mylan objects to the phrase “any other basis,” “all bases,” and “all facts, documents, and circumstances” as being overly broad and requiring the production of trivial documents and other documents with limited, if any, relevance to the parties’ claims or defenses. Mylan further objects to the phrases “at least one valid and enforceable claim,” “one or more claims,” and “each challenged claim” to the extent that this interrogatory seeks information not relevant to the Asserted Claims. Mylan will be responding to this interrogatory only insofar as it is relevant to the claims currently asserted by Plaintiffs. Mylan objects to this interrogatory to the extent it calls for a legal conclusion. Mylan further objects to this interrogatory as premature under the Scheduling Order, as discovery is just beginning, Mylan has not received any discovery from Bayer, and no depositions have been conducted. Mylan further objects to this interrogatory as premature under the Local Rules and the Default Standard for Discovery Including Discovery of ESI, which requires Plaintiffs to produce initial claim charts demonstrating how each product allegedly infringes each asserted patent claim before Defendants provide any initial contentions. This interrogatory essentially requires Mylan to provide non-infringement contentions before Plaintiffs have provided its infringement contentions. Mylan further objects to this interrogatory to the extent that Mylan does not bear the burden of proof regarding infringement, including induced infringement. Mylan further objects to this interrogatory as seeking expert discovery prior to the dates for expert reports. Mylan objects to this interrogatory to the extent it seeks information that is confidential, protected by the right of privacy, and/or protected from disclosure by applicable privileges and protections, including without limitation the attorney-client privilege, work product protection, common interest privilege and/or consulting expert privilege. Mylan objects to this interrogatory to the extent it seeks information the disclosure of which is subject to third-party confidentiality obligations or a protective order. Mylan objects to this interrogatory to the extent it requests information not in Mylan’s possession, custody, or control. Mylan objects to this interrogatory to the extent it calls for information already in Plaintiffs’ possession, or calls for publicly available

information. Mylan objects to this interrogatory as vague and ambiguous as to the term “circumstances.” Mylan proposes that the parties meet and confer to determine a meaning. Mylan objects to this interrogatory to the extent it includes multiple subparts, each of which constitutes a separate Interrogatory pursuant to Fed. R. Civ. P. 33(a)(1). Mylan further objects to this interrogatory as improper under Fed. R. Civ. P. 33(a) because it purports to be a single interrogatory but contains multiple subparts. This interrogatory has at least two discrete subparts and is, therefore, at least two interrogatories. Mylan further objects to the description of this interrogatory as Interrogatory No. 4. Mylan considers this Request to be Interrogatory Nos. 15-16.

Subject to and without waiving the foregoing objections, and to the extent understood, Mylan responds that it is Plaintiffs’ burden to provide initial infringement contentions under the Scheduling Order because infringement is their burden. Mylan will supplement its response after Plaintiffs provide appropriate infringement contentions.

Discovery is on-going and Mylan will supplement its response if necessary and in accordance with the Federal Rules of Civil Procedure. Mylan is available to meet and confer with Plaintiffs to determine an appropriate discovery schedule for the provision of information, documents, and things in accordance with the Scheduling Order, Local Rules for the District of Delaware, the Default Standard for Discovery Including Discovery of ESI, and the Federal Rules of Civil Procedure.

SUPPLEMENTAL RESPONSE TO INTERROGATORY NO. 4:

Mylan incorporates by reference the General Objections, Objections to Definitions and Instructions, and each specific objection set forth above as if fully stated herein. This interrogatory is also premature and improper because it assumes that the Asserted Claims are valid and enforceable, which Mylan contends. Mylan supplements its response to Interrogatory No. 2 as follows:

The manufacture, sale, offer for sale, or importation of Mylan’s ANDA Product do not directly or indirectly infringe the Asserted Claims. As a matter of law, Mylan’s ANDA

Products cannot infringe invalid claims. *Richdel, Inc. v. Sunspool Corp.*, 714 F.2d 1573, 1580 (Fed. Cir. 1983). The Asserted Claims are anticipated, obvious, indefinite, lacks written description, and/or is not enabled. Mylan incorporates by reference its response and supplemental response to Interrogatory No. 1 for each of the Asserted Claims.

INTERROGATORY NO. 5:

Identify all individuals involved in the decision to develop Mylan's ANDA Product and the date on which Mylan decided to proceed with the development of Mylan's ANDA Product.

RESPONSE TO INTERROGATORY NO. 7:

Mylan incorporates the General Objections set forth above. Mylan objects to this interrogatory as overly broad, unduly burdensome, and oppressive to the extent it seeks information that is irrelevant to the claims and defenses at issue in this case and is not proportional to the needs of the case. For example, Mylan objects to the phrase "all individuals" as being overly broad and requiring the production of trivial documents and other documents with limited, if any, relevance to the parties' claims or defenses. Mylan objects to this interrogatory to the extent it seeks information that is confidential, protected by the right of privacy, and/or protected from disclosure by applicable privileges and protections, including without limitation the attorney-client privilege, work product protection, common interest privilege and/or consulting expert privilege. Mylan objects to this interrogatory to the extent it seeks information the disclosure of which is subject to third-party confidentiality obligations or a protective order. Mylan objects to this interrogatory to the extent it requests information not in Mylan's possession, custody, or control. Mylan further objects to this interrogatory as premature under the Scheduling Order, as discovery is just beginning. Mylan objects to this interrogatory as vague and ambiguous as to the phrases "involved in the decision" and "decided to proceed with the development." Mylan proposes that the parties meet and confer to determine a meaning. Mylan objects to this interrogatory to the extent it includes multiple subparts, each of which constitutes a separate Interrogatory pursuant to Fed. R. Civ. P. 33(a)(1). Mylan further objects to this interrogatory as improper under Fed. R. Civ. P. 33(a) because it

purports to be a single interrogatory but contains multiple subparts. This interrogatory has at least two discrete subparts and is, therefore, at least two interrogatories. Mylan further objects to the description of this interrogatory as Interrogatory No. 5. Mylan considers this Request to be Interrogatory Nos. 17-18.

Subject to and without waiving the foregoing objections, and to the extent understood, Mylan responds as follows: pursuant to Rule 33(d) of the Federal Rules of Civil Procedure, Mylan states that it has no information responsive to this interrogatory because Mylan did not develop the ANDA Product.

Discovery is on-going and Mylan will supplement its response if necessary and in accordance with the Federal Rules of Civil Procedure.

OF COUNSEL:

POTTER ANDERSON & CORROON LLP

Douglas H. Carsten
Nellie J. Amjadi
WILSON SONSINI GOODRICH & ROSATI
12235 El Camino Real, Suite 200
San Diego, CA 92130
Tel: (858) 350-2300

Dennis D. Gregory
WILSON SONSINI GOODRICH & ROSATI
1301 Avenue of the Americas, 40th Floor
New York, NY 10019-6022
Tel: (212) 999-5800

Nancy L. Zhang
WILSON SONSINI GOODRICH & ROSATI
650 Page Mill Road
Palo Alto, CA 94304
Tel: (858) 350-2300

Dated: December 20, 2016
1240745 / 42284 (cons.)

By: /s/ Bindu A. Palapura
Richard L. Horwitz (#2246)
David E. Moore (#3983)
Bindu A. Palapura (#5370)
Stephanie E. O'Byrne (#4446)
Hercules Plaza, 6th Floor
1313 N. Market Street
Wilmington, DE 19801
Tel: (302) 984-6000
rhorwitz@potteranderson.com
dmoore@potteranderson.com
bpalapura@potteranderson.com
sobyrne@potteranderson.com

*Attorneys for Defendant Mylan
Pharmaceuticals Inc.*

CERTIFICATE OF SERVICE

I, Bindu A. Palapura, hereby certify that on December 20, 2016, true and correct copies of the within document were served on the following counsel of record at the addresses and in the manner indicated:

VIA ELECTRONIC MAIL

Jack Blumenfeld
Maryellen Noreika
Derek J. Fahnestock
Morris, Nichols, Arsht & Tunnel LLP
1201 North Market Street
P. O. Box 1347
Wilmington, DE 19899
jblumenfeld@mnat.com
mnoreika@mnat.com
dfahnestock@mnat.com

Bruce R. Genderson
Adam L. Perlman
Dov P. Grossman
Jessica Rydstrom
Joelle Perry
Teagan J. Gregory
Christopher S. Geyer
Williams & Connolly LLP
725 Twelfth Street, N.W.
Washington, DC 20005
bgenderson@wc.com
aperlman@wc.com
dgrossman@wc.com
jrydstrom@wc.com
jperry@wc.com
tgregory@wc.com
cgeyer@wc.com

/s/ Bindu A. Palapura

Bindu A. Palapura

EXHIBIT 8

REDACTED
IN ITS
ENTIRETY

EXHIBIT 9

REDACTED
IN ITS
ENTIRETY

EXHIBIT 10



12235 El Camino Real, Suite 200
San Diego, CA 92130-3002
PHONE 858.350.2300
FAX 858.350.2399
www.wsgr.com

November 9, 2015

Via Federal Express

Bayer Healthcare LLC
100 Bayer Blvd
Whippany, NJ 07981

Bayer Intellectual Property GmbH
Creative Campus Monheim
Building, 4865, Alfred Nobel Strabe 10
Monheim, Germany 40789

CONFIDENTIAL

Re: Sorafenib Tosylate
Mylan Pharmaceuticals Inc. ANDA No. 207012
Dosage Form: Tablet
Dosage Strength: 200 mg
Route of Administration: Oral
U.S. Patent Nos. 7,897,623; 7,235,576; 7,351,834; 8,877,933; 8,841,330

Notice of Paragraph IV Certification

Dear Sir or Madam:

This is a notice of certification letter on behalf of Mylan Pharmaceuticals Inc. (“Mylan”) pursuant to § 505(j)(2)(A)(vii) of the Federal Food, Drug and Cosmetic Act (“the Act”) and §§ 314.94 and 314.95 of Title 21 of the Code of Federal Regulations. This letter is provided to Bayer Healthcare LLC (“Bayer”), the holder of approved New Drug Application (“NDA”) No. 21923 Nexavar[®] tablets, 200 mg, and the assignee of U.S. Patent Nos. 7,897,623; 7,235,576; 7,351,834; and 8,841,330. This letter is also provided to Bayer Intellectual Property GmbH, the assignee of U.S. Patent No. 8,877,933.

1. To obtain approval to engage in the commercial manufacture, use or sale of sorafenib tosylate tablets, 200 mg, Mylan, having a principal place of business at 781 Chestnut Ridge Road, Morgantown, WV 26505, submitted to the Food and Drug Administration (“FDA”) an Abbreviated New Drug Application (“ANDA”), which under § 505(j) of the Act contains any required bioavailability or bioequivalence data or information.

2. The ANDA number is 207012.



CONFIDENTIAL

November 9, 2015

Page 2

3. The established name of Mylan's proposed drug is sorafenib tosylate tablets, 200 mg. Bayer markets sorafenib tosylate tablets, 200 mg, under the brand name Nexavar®.

4. The active ingredients, strengths, and dosage form of the proposed drug product is sorafenib tosylate in 200 mg dosage strength intended for oral administration.

5. The ANDA indicates that Mylan seeks to obtain approval to engage in the commercial manufacture, use, or sale of the drug product before expiration of the following U.S. patent, which expires on the below-listed date and is listed in the Food and Drug Administration's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book") for Nexavar® 200 mg:

<u>Patent Number</u>	<u>Orange Book Expiration Date</u>
8,618,141	February 11, 2023
7,897,623	January 12, 2020
7,235,576	January 12, 2020
7,351,834	January 12, 2020
8,877,933	December 24, 2027
8,841,330	January 12, 2020

Mylan has certified to the FDA that the manufacture, use, sale or importation of the drug products that are the subject of the above-referenced ANDA will not infringe any valid claim of the 8,618,141 patent ("the '141 patent"), the 7,897,623 patent ("the '623 patent"), the 7,235,576 ("the '576 patent") patent, the 7,351,834 patent ("the '834 patent"), the 8,877,933 patent ("the '933 patent"), and the 8,841,330 patent ("the '330 patent").

6. A detailed statement of the present factual and legal bases of Mylan's belief that the '141 patent is not valid, unenforceable, and/or will not be infringed was previously provided to Bayer pursuant to U.S.C. § 355(j)(2)(B)(iv)(II) and 21 C.F.R. § 314.95(c)(6) in a letter dated December 19, 2014.

7. A detailed statement of the present factual and legal bases of Mylan's belief that the '623, '576, '834, '933 and the '330 patents are not valid, unenforceable, and/or will not be infringed is attached and is made pursuant to U.S.C. § 355(j)(2)(B)(iv)(II) and 21 C.F.R. § 314.95(c)(6).

8. Wilson Sonsini Goodrich & Rosati P.C. is authorized to accept service of process for Mylan, solely relating to ANDA No. 207012. Please direct any correspondence in this regard to my attention.

9. An Offer of Confidential Access is attached.

The information in this letter and its attachments are supplied for the sole purpose of complying with the above-referenced statutes and regulations. Neither Mylan nor its attorneys



CONFIDENTIAL
November 9, 2015
Page 3

waive any attorney-client privilege or work product immunity concerning the subject matter of this communication.

Reservation of Legal Right

Mylan reserves the right to assert the same, similar, different or new theories of non-infringement, invalidity and/or unenforceability and nothing in this Notice Letter or Detailed Statement shall be construed as to limit Mylan's right to make any allegation in any subsequent litigation regarding any issue.

Sincerely,

WILSON SONSINI GOODRICH & ROSATI
Professional Corporation



Douglas Carsten

Encl.: Detailed Statement of Factual and Legal Bases for Mylan's Paragraph IV Certification concerning U.S. Patent Nos. 7,897,623; 7,235,576; 7,351,834; 8,877,933; 8,841,330.

Offer of Confidential Access

**DETAILED STATEMENT OF THE FACTUAL AND LEGAL BASES FOR
MYLAN PHARMACEUTICALS INC.'S PARAGRAPH IV CERTIFICATION WITH
RESPECT TO U.S. PATENT NOS. 7,897,623; 7,235,576; 7,351,834; 8,877,933; 8,841,330**

The manufacture, use, offer to sell, sale, or import of Mylan Pharmaceuticals Inc.'s ("Mylan") proposed sorafenib tosylate tablets, 200 mg, that are the subject of ANDA No. 207012 would not infringe any valid and enforceable claim of U.S. Patent Nos. 7,897,623; 7,235,576; 7,351,834; 8,877,933; and 8,841,330.

I. Legal Standards

A. Patent Invalidity

A patent is invalid if it fails to satisfy any of the conditions for patentability found in 35 U.S.C. §§ 101 *et seq.* It is axiomatic that an invalid patent cannot be infringed. *See TypeRight Keyboard Corp. v. Microsoft Corp.*, 374 F.3d 1151, 1157 (Fed. Cir. 2004) (holding that a finding of invalidity is a complete defense to infringement); *Viskase Corp. v. Am. Nat'l Can Co.*, 261 F.3d 1316, 1329 (Fed. Cir. 2001) (same); *see also Weatherchem Corp. v. J.L. Clark Inc.*, 163 F.3d 1326, 1335 (Fed. Cir. 1998) ("[I]nvalidity operates as a complete defense to infringement for any product, forever.").

1. Burden of Proof and Presumption of Validity

The burden of proving invalidity rests with the party asserting it. "A patent, though presumed valid, 35 U.S.C. § 288 (1988), is actually a fragile entity, and must be propped up by a myriad of supports, each representative of one of the legal requirements of validity. If even a single one of these supports is removed, the patent will fall. For example, a patent may be declared invalid . . . if it is found to be anticipated by a prior art reference, *see id.* § 102; if it is rendered obvious by a combination of the prior art, *see id.* § 103; or if it fails to satisfy any one of a number of a variety of other conditions." *Morton Int'l Inc. v. Cardinal Chem. Co.*, 5 F.3d 1464, 1471-72 (Fed. Cir. 1993) (Mayer, J., concurring).

The statutory presumption of validity merely assumes the PTO properly did its job by considering all prior art or other evidence material to patentability. *See Lannom Mfg. Co. v. U.S. Int'l Trade Comm'n*, 799 F.2d 1572, 1575 (Fed. Cir. 1986). "[W]here the PTO has not considered facts relevant to an issue in suit, there is no reason to give deference to its action in issuing the patent and a court may find those facts controlling in determining whether the burden of proof has been sustained." *Kalman v. Kimberly-Clark Corp.*, 713 F.2d 760, 773 n.3 (Fed. Cir. 1983), *overruled on other grounds by SRI Intl v. Matsushita Elec. Corp. of Am.*, 775 F.2d 1107 (Fed. Cir. 1985). Thus, "[t]he courts are the final arbiter of patent validity and, although courts may take cognizance of, and benefit from, the proceedings before the patent examiner, the question is ultimately for the courts to decide, without deference to the rulings of the patent

examiner.” *Quad Envtl. Techs. Corp. v. Union Sanitary Dist.*, 946 F.2d 870, 876 (Fed. Cir. 1991).

2. 35 U.S.C. § 102-Anticipation

Under § 102, a person shall be entitled to a patent unless “the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for patent,” 35 U.S.C. § 102(a), or “the invention was patented or described in a printed publication in this country or a foreign country . . . more than one year prior to the date of the application for patent in the United States,” *id.* § 102(b).

A patent claim is said to be anticipated (i.e., not novel) if a comparison of the claim with a prior art reference reveals that every element of the claim is described, either expressly or inherently, in the prior art reference. *See In re King*, 801 F.2d 1324, 1326 (Fed. Cir. 1986); *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1346 (Fed. Cir. 2002); *Schering Corp. v. Geneva Pharms.*, 339 F.3d 1373, 1377 (Fed. Cir. 2003). “Under the principles of inherency, if the prior art necessarily functions in accordance with, or includes, the claimed limitations, it anticipates.” *Mehl/Biophile Intl Corp. v. Milgraum*, 192 F.3d 1362, 1365 (Fed. Cir. 1999).

3. U.S.C. § 102(e)-Prior Art

Under § 102(e), a person shall be entitled to a patent unless “the invention was described in - (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent,” *id.* § 102(e).

A § 102(e) reference is effective as not only as of its filing date, but as to the filing date of a provisional application it claims § 119(e) priority to where that provisional application provides § 112 support for the subject matter in issue. *See In re Giacomini*, 612 F.3d 1380 (Fed. Cir. 2010); *Ex Parte Takako Yamaguchi ex rel. Katsumi Yamaguchi, and Tomohiro Okazaki*, 2008 WL 4233306 (Bd. Pat. App. & Interferences 2008) (*precedential*); MPEP 2136.03.

4. 35 U.S.C. § 112 – Written Description

35 U.S.C. § 112, paragraph one, states, in part:

[t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same.

35 U.S.C. § 112 (2000). The Federal Circuit has stated that “the description must ‘clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.’” *Ariad v. Eli Lilly*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (*en banc*, quoting *In re Gosteli*, 872 F.2d 1008, 1012 (Fed. Cir. 1989)). “The test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Id.*

The test for possession “requires an objective inquiry into the four corners of the specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe an invention understandable to that skilled artisan and show that the inventor actually invented the invention claimed.” *Id.*

The Federal Circuit provided further details on the inquiry: “[T]he written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement.” *Id.* at 1352. “Conversely, we have repeatedly stated that actual ‘possession’ or reduction to practice outside the specification is not enough. Rather, as stated above, it is the specification itself that must demonstrate possession.” *Id.* Furthermore, “a description that merely renders the invention obvious does not satisfy the requirement,” and that “a vague functional description and an invitation for further research does not constitute written disclosure of a specific inhibitor.” *Id.* at 1352, 1356. With respect to claimed methods of using certain molecules, prophetic examples may be used but “mere mention of a desired outcome” is insufficient to satisfy the written description requirement. *Id.* at 1357.

5. 35 U.S.C. § 103(a)-Obviousness

Under § 103(a), “[a] patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a).

Obviousness is ultimately a legal conclusion, based upon underlying factual inquiries. *McNeil-PPC, Inc. v. L. Perrigo Co.*, 337 F.3d 1362, 1368 (Fed. Cir. 2003). The required factual inquiry asks: (1) what was the scope and content of the prior art; (2) what are the differences between the prior art and the asserted claims; and (3) what is the level of ordinary skill in the pertinent art. *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966).

Further, courts have held that a previously cited prior art reference should not be entirely disregarded because it had been previously considered by the USPTO and overcome by the Applicants. *In re Swanson*, 540 F.3d 1368; (BNA) 1196, 1201 (Fed. Cir. 2007) *citing* 35 U.S.C. § 303(a) (2002). Instead “the PTO should evaluate the context in which the reference was previously considered and the scope of the prior consideration and determine whether the

reference is *now being considered for a substantially different purpose.*" *Id.*, emphasis added. "Determining the scope of an examiner's previous consideration of a reference will generally require an analysis of the record of the prior proceedings to determine if and how the examiner used the reference in making his initial decisions." *Id.* at 88; U.S.P.Q.2d (BNA) 1205.

For patents claiming purportedly one or more new chemical compounds, such compounds are *prima facie* obvious if (1) a person of ordinary skill in the art would have selected prior art compounds as lead compounds, and (2) a reason or motivation for modifying the lead compounds to make the claimed compound with a reasonable expectation of success can be found in the prior art. *Otsuka Pharmaceutical Co. v. Sandoz, Inc.*, 678 F.3d 1280 (Fed. Cir. 2012).

Finally, objective evidence of non-obviousness, i.e., so-called "secondary considerations," is considered where relevant. *Graham*, 383 U.S. at 17. When, from the perspective of a person of ordinary skill in the art, the differences between the prior art and the claimed invention as a whole would be obvious, a *prima facie* case of obviousness is established under § 103. *See In re Dillon*, 919 F.2d 688, 692-93 (Fed. Cir. 1990). The patentee then has the burden of coming forward with rebuttal evidence of secondary considerations to support an assertion of non-obviousness. *See Ecolochem, Inc. v. Southern Cal. Edison Co.*, 227 F.3d 1361, 1381 (Fed. Cir. 2000). In addition, the patentee must establish a causal relation or "nexus" between the purported invention and the secondary consideration to support a finding of non-obviousness. *See Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005).

6. Level of Ordinary Skill in the Art

The hypothetical person of ordinary skill in the art is neither a person who is extraordinarily innovative, nor a researcher of inexhaustible patience but is a person who thinks conventionally in matters affecting the art in which he or she is skilled. *Standard Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 454 (Fed. Cir. 1985). "Ordinary skill means at least the ability to understand the technology and make modest adaptations or advances." *See In re Mahurkar Patent Litg.*, 831 F. Supp. 1354, 1374 (N.D. Ill. 1993), *aff'd* 71 F.2d 1573 (Fed. Cir. 1995). Factors that may be considered for determining the level of a skilled practitioner include:

- 1) the educational level of the inventor;
- 2) types of problems encountered in the art;
- 3) prior art solutions to these problems;
- 4) rapidity with which innovations are made;
- 5) sophistication of the technology; and

6) educational level of active workers in the field.

Daiichi Sankyo, Ltd. v. Apotex, Inc., 501 F.3d 1254, 1256 (Fed. Cir. 2007) (citation omitted). The hypothetical person of ordinary skill in the art is presumed to be aware of all pertinent prior art. *See, e.g., Standard Oil Co.*, 774 F.2d at 454.

7. Scope and Content of the Prior Art

As an initial inquiry under *Graham*, the scope and content of the prior art must be considered. *Eolas Techs. Inc. v. Microsoft Corp.*, 399 F.3d 1325, 1335 (Fed. Cir. 2005) (citation omitted); *see also* MPEP §2144.08. A prior art reference is relevant if it is reasonably pertinent to the problem being addressed. *See In re ICON Health and Fitness, Inc.*, 496 F.3d 1374, 1379-80 (Fed. Cir. 2007). "A reference is reasonably pertinent if, even though it may be in a different field from that of the inventor's endeavor, it is one which, because of the matter with which it deals, logically would have commended itself to an inventor's attention in considering his problem." *Id.* (quoting *In re Clay*, 966 F.2d 656, 659 (Fed. Cir. 1992)). A party's admissions may also create valid prior art. *See, e.g., In re Fout*, 675 F.2d 297, 300 (C.C.P.A. 1982) (citation omitted). All disclosures of the prior art, including non-preferred embodiments, must be considered in determining the scope and content of the prior art. *Merck & Co. v. Biocraft Labs.*, 874 F.2d 804, 807 (Fed. Cir. 1989). A patent may be found to be anticipated or obvious over a reference that had properly been before the Patent Examiner in the United States Patent and Trademark Office when the patent issued. *IPXL Holdings, L.L.C. v. Amazon.com, Inc.*, 430 F.3d 1377, 1381 (Fed. Cir. 2005).

8. Differences Between the Prior Art and the Claimed Invention

The differences between the prior art and the scope of the claimed invention must also be ascertained to determine those aspects of the claimed subject matter that may be obvious or nonobvious against the prior art and the knowledge of a skilled artisan. *Graham*, 383 U.S. at 22-23; *see also Dystar Textilfarben GmbH & Co. v. Deutschland KG v. C.H. Patrick Co.*, 464 F.3d 1356, 1369 (Fed. Cir. 2006). The degree of differences between the prior art and the claimed invention may be useful to a reviewing court in determining whether an invention is obvious. *See Graham*, 383 U.S. at 36-37.

9. Objective Indicia of Nonobviousness

A patentee may rebut a *prima facie* case of obviousness through demonstration of objective indicia (also known as secondary considerations) of nonobviousness. *See, e.g., In re Fielder*, 471 F.2d 640, 642-43 (C.C.P.A. 1973) (citations omitted). Such factors include:

- Commercial success
- Long felt but unresolved need
- Licenses showing industry respect

- Copying
- Failure of others in the field
- Unexpected results
- Unexpected properties
- Skepticism of skilled artisans before the invention

See In re Rouffet, 149 F.3d 1350, 1355 (Fed. Cir. 1998) (citing *Graham*, 383 U.S. at 17-18; *In re Mayne*, 104 F.3d 1339, 1342 (Fed. Cir. 1997); *Arkie Lures, Inc. v. Gene Larew Tackle, Inc.*, 119 F.3d 953, 957 (Fed. Cir. 1997); *In re Huang*, 100 F.3d 135, 139-40 (Fed. Cir. 1996); *In re Woodruff* 919 F.2d 1575, 1578 (Fed. Cir. 1990); *Pentec, Inc. v. Graphic Controls Corp.*, 776 F.2d 309, 316 (Fed. Cir. 1985); and *In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988)). Any evidence, however, of secondary considerations must have a sufficient "nexus" with the claimed invention. *See, e.g., Stratoflex*, 713 F.2d at 1539. The patentee ultimately bears this burden of demonstrating a nexus connection with the claimed invention. *See, e.g., In re GPAC*, 57 F.3d 1573, 1580 (Fed. Cir. 1995); *see also In re Comiskey*, 499 F.3d 1365 (Fed. Cir. 2007).

B. Patent Infringement

6. Literal Infringement

Proof of direct infringement is necessary for any patent infringement action. For direct infringement, 35 U.S.C. §271(a) provides that "whoever without authority makes, uses, offers to sell or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefore, infringes the patent."

To determine direct infringement of a patent's claim, a two-step process is used. First, the claim must be properly construed to determine its scope and meaning. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). Second, the accused product, device, or process must be compared to the claim as properly construed. *Id.* To be liable for direct infringement, the accused product, device, or process must contain every limitation of the asserted claim (or its equivalent) to infringe. *Becton Dickinson & Co. v. C.R. Bard, Inc.*, 922 F.2d 792, 796 (Fed. Cir. 1990). The patentee bears the burden of proving patent infringement and must demonstrate infringement by a preponderance of the evidence. *SRI Int'l v. Matsushita Elec. Corp.*, 775 F.2d 1107, 1123 (Fed. Cir. 1985).

a. Claim Construction

Determination of infringement of a patent requires construction of the meaning of the patent's claims and then application of the claims as construed to the accused product or process. *See e.g., Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454 (Fed. Cir. 1998). Interpretation of patent claims is a matter of law reserved for the court. *See Markman v. Westview Instruments*, 52 F.3d 967, 979 (Fed. Cir. 1995) (*en banc*), *aff'd*, 517 U.S. 370 (1996). The general rule is that claim language is given its ordinary and accustomed meaning as understood by one of ordinary



CONFIDENTIAL
November 9, 2015
Page 10

skill in the art, unless the patentee ascribed a different meaning to a claim in either the specification or the prosecution history. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312, 1321 (Fed. Cir. 2005); *Hockerson-Halberstadt, Inc. v. Avia Group Int'l*, 222 F.3d 951, 955 (Fed. Cir. 2000). The starting point for any claim construction must be the claims themselves. *See e.g., Pitney Bowes, Inc. v. Hewlett-Packard Co.*, 182 F.3d 1298, 1305 (Fed. Cir. 1999). In addition to the claims, the courts consider the specification and the prosecution history. *See also Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). The specification sets forth the best mode contemplated by the inventor for carrying out his invention. This one embodiment, however, does not restrict the claims. Claim interpretation must not make use of “best mode” terms inasmuch as the patentee need not guard against infringement by listing every possible infringing device in the specification. *See Adams v. U.S.*, 330 F.2d 622 (Ct. Cl. 1964), *aff’d*, 383 U.S. 39 [citations omitted] (1966). Claims, however, may not be construed one way in order to obtain their allowance and in a contrary way against infringers. *See Autogiro Co. of Am. v. U.S.*, 384 F.2d 391, 396, (Ct. Cl. 1967).

Claim meaning derives from the context in which patent claim language is used. The context includes the specification, other claims in the patent, and the record of the examination proceedings that led to the issuance of the patent. *See e.g., Graham v. John Deere Co.*, 383 U.S. 1, 33 (1966); *Pall Corp. v. Hemasure Inc.*, 181 F.3d 1305, 1308 (Fed. Cir. 1999). The specification “is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.” *Phillips*, 415 F.3d at 1315 (citing *Vitronics*, 90 F.3d at 1582). “The specification is, thus, the primary basis for construing the claims.” *Phillips*, 415 F.3d at 1315 (citing *Stand. Oil Co. v. Am. Cyanamid Co.*, 774 F.2d 448, 452 (Fed. Cir. 1985)). (“[I]t is fundamental that claims are to be construed in the light of the specifications and both are to be read with a view to ascertaining the invention.”). The courts may also use the prosecution history to interpret and understand the language used in the claims. The use of the prosecution history to interpret claim language is distinct from prosecution history estoppel, which is a limitation on the doctrine of equivalents. *See Markman*, 52 F.3d at 1024. The prosecution history limits the interpretation of claim terms so as to exclude any interpretation that was disclaimed during prosecution. *See Southwall Techs. Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1576 (Fed. Cir. 1995). The prior art may also be relevant in the construction of patent claims. Prior art references are most relevant when they are cited in the patent’s specification or prosecution history. *See Jenmar Corp. v. Pattin Mfg. Co.*, 20 USPQ2d 1721, 1726 (S.D. Ohio 1991).

If the preamble breathes life and meaning into the claims, the preamble can further limit the meaning of the claims. *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994). The facts in each case inform the determination of whether a preamble limits a claim on a case-by-case basis; there is no formula defining when a preamble limits the scope of a claim. *See e.g., Catalina Mktg. Intl v. Coolsavings. com, Inc.*, 289 F.3d 801, 808 (Fed. Cir. 2002). “[A] claim preamble has the import that the claim as a whole suggests for it.” *Bell Commc’ns Research, Inc. v. Vitalink Commc’ns Corp.*, 55 F.3d 615, 620 (Fed. Cir. 1995).

b. Comparison of the Accused Composition(s) and Method(s) with the Construed Claims

Once the claim has been construed, it must be applied to the accused device or method. *See Autogiro Co. of Am.*, 384 F.2d at 399-400. It is well settled that each element of a claim is material and essential, and that in order for a court to find infringement, the plaintiff must show the presence of every element or its substantial equivalent in the accused device. *Id.* at 403. *See also Engel Industries, Inc. v. Lockformer Co.*, 96 F.3d 1398, 1405 (Fed. Cir. 1996).

Further, an ANDA that does not seek approval for a patented method of using a drug does not infringe and cannot induce infringement. *See Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1321-22 (Fed. Cir. 2012).

7. Infringement Under the Doctrine of Equivalents

If an accused product or process is found not to literally infringe a claim, it must further be determined whether the claims are infringed under the doctrine of equivalents. "The scope of a patent is not limited to its literal terms but instead embraces all equivalents to the claims described." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co. Ltd.*, 535 U.S. 722, 732 (2002) ("*Festo VIII*"), *on remand to*, 344 F.3d 1359 (Fed. Cir. 2003) ("*Festo X*"). To prove infringement under the doctrine of equivalents, the patentee must show that an accused product or process contains every element of the patented invention or its substantial equivalent. *Warner-Jenkinson Co, Inc. v. Hilton Davis Chemical Co.*, 520 U.S. 17, 40 (1997).

In analyzing elements of a claim to determine equivalency, a court should apply the test originally set down by the Supreme Court in *Graver Tank & Mfg. Co., Inc. v. Linde Air Prods Co.*, 339 U.S. 605, 608-610 (1950), as to whether the element performs substantially the same function in substantially the same way to achieve substantially the same result. *See e.g., Warner-Jenkinson Co. v. Hilton Davis Chem. Co.*, 520 U.S. 17, 38 (1997). This test is applied after the claim elements or steps are first determined and whether they correspond to an accused product or process.

"The scope of a patent is not limited to its literal terms but instead embraces all equivalents to the claims described." *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 732 (2002). "[A] patentee may invoke this doctrine [of equivalents] to proceed against the producer of a device 'if it performs substantially the same function in substantially the same way to obtain the same result'." *Graver Tank & Mfg. Co., Inc.*, 339 U.S. at 608 (citation omitted). "The doctrine of equivalents allows the patentee to claim those insubstantial alterations that were not captured in drafting the original patent claim but which could be created through trivial changes." *Festo Corp.*, 535 U.S. at 733.



CONFIDENTIAL
November 9, 2015
Page 12

With regard to means-plus-function claims “[a]n accused structure that does not literally infringe a means-plus-function claim may nevertheless infringe under the doctrine of equivalents”

Lockheed Martin Corp. v. Space Systems/Loral, Inc., 324 F.3d 1308, 1318 (Fed. Cir. 2003). “[A]n accused device can infringe under the doctrine of equivalents without infringing literally under 35 U.S.C. § 112, Para. 6 because the doctrine only requires substantially the same function, not identically of the function as in Section 112, Para. 6.” *WMS Gaming*, 184 F.3d 1339, 1353 (Fed. Cir. 1999). In a situation, however, where an element is not found to be equivalent structure under 35 U.S.C. § 112, sixth paragraph and does not involve later-developed technology, “a finding of non-equivalence for Section 112, Para. 6, purposes should preclude a contrary finding under the doctrine of equivalents.” *Chiuminatta Concrete Concepts Inc. v. Cardinal Industries Inc.*, 145 F.3d 1303, 1311 (Fed. Cir. 1998).

“[T]he determination of infringement under the doctrine of equivalents is limited by two primary legal doctrines: (1) prosecution history estoppel and (2) the ‘all elements’ rule.” *Lockheed Martin Corp.*, 324 F.3d at 1318. Furthermore,

Estoppel arises when an amendment is made to secure the patent and the amendment narrows the patent’s scope. ... A patentee who narrows a claim as a condition for obtaining a patent disavows his claim to the broader subject matter, whether the amendment was made to avoid the prior art to comply with § 112. We must regard the patentee as having conceded an inability to claim the broader subject matter or at least as having abandoned his right to appeal a rejection. In either case estoppel may apply.

Festo Corp., 535 U.S. at 736-37. “[A] narrowing amendment should [not] be deemed to relinquish equivalents unforeseeable at the time of the amendment and beyond a fair interpretation of what was surrendered. Nor is there any call to foreclose claims of equivalence for aspects of the invention that have only a peripheral relation to the reason the amendment was submitted.” *Id.* at 738. “[T]he patentee should bear the burden of showing that the amendment does not surrender the particular equivalent in question.” *Id.* at 740.

“Under the all elements rule, there can be no infringement under the doctrine of equivalents if even one limitation of a claim or its equivalent is not present in the accused device.” *Lockheed Martin Corp.*, 324 F.3d at 1321.

Each element contained in a patent claim is deemed material to defining the scope of the patented invention, and thus the doctrine of equivalents must be applied to individual elements of the claim, not to the invention as a whole. It is important to ensure that the application of the doctrine,



CONFIDENTIAL
November 9, 2015
Page 13

even as to an individual element, is not allowed such broad play as to effectively eliminate that element in its entirety.

Warner-Jenkinson Co., 520 U.S. at 30.

II. U.S. Patent No. 7,351,834

U.S. Patent Number 7,351,834 (“the ’834 patent”) entitled “ ω -Carboxyaryl substituted diphenyl ureas as raf kinase inhibitors” issued April 1, 2008, from application U.S. Serial No. 09/889,227, (the ’227 application) filed on January 12, 2000, filed as the National Stage entry of PCT/US2000/00648 filed on January 12, 2000, which is a continuation-in-part of U.S. Serial No. 09/425,228 (’228 application) filed on October 22, 1999, which is a continuation-in-part of U.S. Serial No. 09/257,266 (’266 application), filed on February 25, 1999, and claiming priority from U.S. Provisional Application No. 60/115, 877 (’877 provisional application) filed on January 13, 1999.

According to the specification, the ’834 patent discloses compounds that are inhibitors of the enzyme raf kinase. These inhibitors play a role in the treatment of tumors and/or cancerous cell growth where inhibition of the raf kinase pathway is indicated. ’834 patent at col. 1, ll. 55-61. In particular, the ’834 patent is directed to the use of a group of aryl ureas in treating raf mediated diseases, and pharmaceutical compositions for use in such therapy. *Id.* at col. 1, ll. 14-16. The patent is directed towards both aryl and heteroaryl analogues, compositions, and methods for treating a raf-mediated disease in humans or mammals. *Id.* at col. 2, ll. 5-13. Sorafenib (N-(4-chloro-3-(trifluoromethyl)phenyl)-N’-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea) is disclosed in as compound entry no. 42. *Id.* at col. 71-72, Table 4.

As detailed further below, the forty-one claims of the ’834 patent are generally directed to compounds and pharmaceutically acceptable salts thereof.

A. Claims of the ’834 Patent

The ’834 patent issued with forty-one claims, including five independent claims (claims 1, 24, 25, 35, and 39), which read as follows:

1. A compound of Formula I



or a pharmaceutically acceptable salt thereof, wherein



A is a substituted moiety of the formula:



wherein L is phenyl, optionally substituted by halogen, up to per-halo, and W_n, where n is 0-3;



CONFIDENTIAL
November 9, 2015
Page 15

wherein each W is independently selected from the group consisting of C₁-C₅ linear or branched alkyl, C₁-C₅ linear or branched haloalkyl up to perhaloalkyl and C₁-C₃ alkoxy L¹ is selected from pyridinyl substituted by —C(O)R_x, and

optionally substituted with 1-3 additional substituents independently selected from the group consisting of R⁷ and halogen;

wherein R_x is NR_aR_b and R_a and R_b are

A) independently

- a) hydrogen,
- b) C₁-C₁₀ alkyl,
- c) C₆ aryl,
- d) pyridinyl
- e) substituted C₁₋₁₀ alkyl,
- f) substituted C₆ aryl,
- g) substituted pyridinyl
- h) -phenylpiperazine(pyridinyl),
- i) -phenylmorpholinyl,
- j) -ethylmorpholinyl,
- k) -ethylpiperidyl,
- l) -methyl pyrrolidinyl,
- m) -methyl tetrahydrofuryl,
- or
- n) —C₂H₄NH(phenyl);



CONFIDENTIAL
November 9, 2015
Page 16

where when R_a and R_b are a substituted group, they are substituted by

- a) halogen up to per halo,
- b) hydroxy,
- c) $—N(CH_3)_2$,
- d) C_1-C_{10} alkyl,
- e) C_1-C_{10} alkoxy,
- f) halosubstituted C_{1-6} alkyl, or
- g) $—OSi(Pr-i)_3$; or

B) R_a and R_b together form piperazine or a substituted piperazine with substituents selected from the group consisting of

- a) halogen,
- b) hydroxy,
- c) C_{1-10} alkyl,
- d) pyridinyl
- e) C_{1-10} alkoxy,
- f) C_6 aryl,
- g) halo substituted C_6 aryl, and
- h) N-(4-acetylphenyl);

M is selected from the group consisting of oxygen and sulfur;

and

B is

phenyl, substituted with 1-3 substituents independently selected from the group consisting of halogen and R⁷,

and R⁷ is

(a) C₁-C₆ linear or branched alkyl, optionally substituted with 1-3 halogen substituents; or

(b) C₁-C₆ linear or branched alkoxy.

2. A compound as in claim 1 wherein M is oxygen.
3. A compound as in claim 1 wherein the cyclic structures of B and L bound directly to D are substituted in the ortho position by hydrogen.
4. A compound of claim 1 wherein B of Formula I is phenyl, substituted with 1-3 substituents independently selected from the group consisting of chlorine, C₁-C₆ alkoxy or up to per halo substituted C₁-C₆ alkyl.
5. A compound of claim 2 wherein B of Formula I is phenyl, substituted with 1-3 substituents independently selected from the group consisting of chlorine, C₁-C₆ alkoxy, or substituted C₁-C₆ alkyl, substituted by one or more halogen substituents.
6. A compound of claim 3 wherein B of Formula I is phenyl, substituted 1 to 3 times by 1 or more substituents selected from the group consisting of chlorine, C₁-C₆ alkoxy or up to per halo substituted C₁-C₆ alkyl.
7. A compound of claim 1, wherein L is phenyl, optionally substituted by halogen up to perhalo.
8. A compound of claim 1, wherein L is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of halogen and C₁-C₃ alkoxy.
9. A compound of claim 3, wherein M is —O—.
10. A compound of claim 6 wherein M is —O—.
11. A compound of claim 7 wherein M is —O—.
12. A compound of claim 8 wherein M is —O—.
13. A compound of claim 1 wherein L₁ is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C₁-C₆ alkyl, halogen and C₁-C₆ alkoxy.

14. A compound of claim 2 wherein L1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C1-C6 alkyl, halogen and C1-C6 alkoxy.
15. A compound of claim 9 wherein L1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C1-C6 alkyl, halogen and C1-C6 alkoxy.
16. A compound of claim 10 wherein L1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C1-C6 alkyl, halogen and C1-C6 alkoxy.
17. A compound of claim 11 wherein L1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C1-C6 alkyl, halogen and C1-C6 alkoxy.
18. A compound of claim 12 wherein L1 is additionally substituted 1 to 3 times by one or more substituents selected from the group consisting of C1-C6 alkyl, halogen and C1-C6 alkoxy.
19. A compound of claim 2 wherein Ra and Rb are independently hydrogen or C1-C6 alkyl.
20. A compound of claim 9 wherein Ra and Rb are independently hydrogen or C1-C6 alkyl.
21. A compound of claim 10 wherein Ra and Rb are independently hydrogen or C1-C6 alkyl.
22. A compound of claim 11 wherein Ra and Rb are independently hydrogen or C1-C6 alkyl.
23. A compound of claim 12 wherein Ra and Rb are independently hydrogen or C1-C6 alkyl.

24. A compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein

D is $-\text{NH}-\text{C}(\text{O})-\text{NH}-$,

A is of the formula: $-\text{L}-\text{M}-\text{L}^1$, wherein

L is phenyl, optionally substituted with 1-3 substituents independently selected from the group consisting of C₁-C₅ linear or branched alkyl, C₁-C₅ linear or branched haloalkyl up to perhalo, C₁-C₃ alkoxy and halogen;

L¹ is pyridinyl, substituted by $-\text{C}(\text{O})\text{R}_x$;

wherein R_x is NR_aR_b and R_a and R_b are independently

hydrogen,

C_1 - C_{10} alkyl,

C_6 aryl,

pyridinyl, substituted C_{1-10} alkyl,

substituted C_6 aryl, or

substituted pyridinyl,

where R_a and R_b are a substituted group, they are substituted by halogen up to per halo; and

M is selected from the group consisting of oxygen and sulfur

and

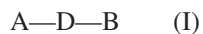
B is phenyl, substituted with 1-3 substituents independently selected from the group consisting of R^7 and halogen;

and R^7 is

(a) C_1 - C_6 linear or branched alkyl, optionally substituted with 1-3 halogen substituents; or

(b) C_1 - C_6 linear or branched alkoxy.

25. A compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein

D is $-NH-C(O)-NH-$,

A is of the formula: $-L-M-L^1$,

L is phenyl,

M is $-O-$,

L^1 is pyridinyl substituted by —C(O)R_x ,

wherein R_x is NR_aR_b and R_a and R_b are independently

hydrogen,

$\text{C}_1\text{--C}_{10}$ alkyl,

C_6 aryl,

pyridinyl,

substituted C_{1-10} alkyl,

substituted C_6 aryl, or

substituted pyridinyl

where R_a and R_b are a substituted group, they are substituted by halogen up to per halo,

and

B is a phenyl group substituted by trifluoromethyl or tert-butyl, and optionally additional substituents selected from the group consisting of halogen up to per halo, and W_n where n is 0-3, and each W is independently selected from the group consisting of

$\text{C}_1\text{--C}_{10}$ alkyl,

$\text{C}_1\text{--C}_{10}$ alkoxy,

C_6 aryl,

pyridinyl,

and substituted $\text{C}_1\text{--C}_{10}$ alkyl, substituted by one or more substituents independently selected from the group consisting of halogen up to per halo.

26. A compound as in claim 24 wherein the cyclic structures of B and L bound directly to D are substituted in the ortho position by hydrogen.



CONFIDENTIAL

November 9, 2015

Page 21

27. A compound as in claim 25 wherein the cyclic structures of B and L bound directly to D are substituted in the ortho position by hydrogen.
28. A compound as in claim 24 wherein substituents for B, are selected from the group consisting of up to per halo substituted C1-C6 alkyl and halogen.
29. A compound as in claim 25 wherein the optional substituents for B are selected from the group consisting of up to per halo substituted C1-C6 alkyl and halogen.
30. A pharmaceutically acceptable salt of a compound of formula I of claim 1 which is
- a) a basic salt of an organic acid or inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or
 - b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.
31. A pharmaceutically acceptable salt of a compound of claim 24 which is
- a) a basic salt of an organic acid or inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or
 - b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.
32. A pharmaceutically acceptable salt of a compound of claim 25 which is
- a) a basic salt of an organic acid or inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid,

trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or

b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.

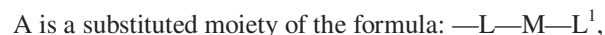
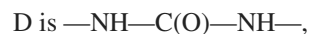
33. A compound of claim 1 wherein the optional substituents on L1 are selected from the group consisting of methyl, trifluoromethyl, methoxy, Cl and F.

34. A compound of claim 1 wherein the substituents of B and L are independently selected from the group consisting of methyl, trifluoromethyl, tert-butyl, methoxy, Cl, and F.

35. A compound of Formula I:



or a pharmaceutically acceptable salt thereof, wherein



wherein L is phenyl, optionally substituted with chlorine or methyl substituents;

L^1 is pyridinyl, substituted with $-C(O)NR^aR^b$;

wherein R^a and R^b independently are

a) hydrogen

b) methyl;

c) ethyl; or

d) propyl

B is phenyl, substituted by tert-butyl or trifluoromethyl and optionally substituted with additional substituents independently selected from the group consisting of

a) halogen, or

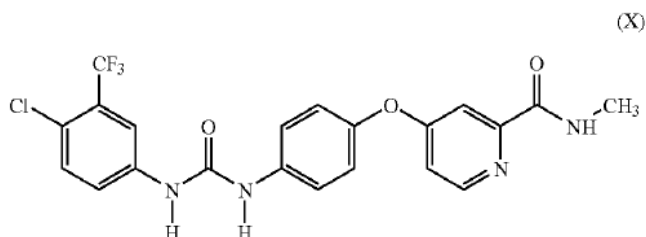
b) methoxy.

36. A compound of claim 35 where L has no optional substituents.

37. A compound of claim 35 where R^a is hydrogen and R^b is methyl.

38. A compound of claim 35 where B is substituted by trifluoromethyl and chlorine or bromine.

39. A compound which is N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula X



40. A compound of claim 39 which is a pharmaceutically acceptable salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea that is a basic salt of an organic acid or an inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid.

41. A compound of claim 39 which is a tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea.

B. Prosecution History of the '834 Patent

i. Application as Filed

On January 12, 2000, International Application No. PCT/US2000/00648 entered the U.S. national stage as the '227 application, which was filed with sixty seven original claims directed to sorafenib generically and as specie.

ii. October 31, 2002 Restriction/Election Requirement and December 19, 2002 Response

The Examiner identified 15 separate inventions not related to a single inventive concept. In the December 19, 2002 Response, the Applicants elected with traverse Group IV (claims 1-67 in part), drawn to compounds, pharmaceutical compositions and method of treating using compounds of Formula I, wherein A is L-M-L', wherein M is oxygen or sulphur, L is phenyl and L' is phenyl, pyridinyl or pyrimidinyl, and B is phenyl, substituted at least by a tert-butyl group or a trifluoromethyl group.

iii. January 17, 2003 Non-Final Office Action and July 21, 2003 Amendment

In a January 17, 2003 Non-final Office Action, the Examiner rejected claims 1, 18-21, 33, 35-39, 48, 49 are rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement and written description. Claims 60 and 66 were rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Claims 1-67 were provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-67 of copending U.S. Application Serial No. 09/948,915.

In a July 21, 2003 Amendment, the Applicants traversed both rejections under 35 U.S.C. § 112, first and second paragraphs, alleging that the Examiner failed to provide sufficient evidence to support these rejections.

iv. October 15, 2003 Final Rejection and February 19, 2004 Response

In an October 15, 2003 Final Rejection, the Examiner finally rejected the claims repeating the rejection in the previous Office Action primarily on the grounds that the claim language did not encompass only the compounds exemplified in the Examples.

In a February 19, 2004 Response, the Applicants amended both the specification and claims to conform to the language found in the first priority document, U.S. Provisional Application No. 60/115,877 and declined specifically to claim priority to USSN 09/425,228 and 09/257,266. The Applicants also traversed the outstanding 35 U.S.C. § 112, first paragraph and second paragraph rejections. They argued that the specification provided ample guidance on how to prepare compounds encompassed by the original claims as well as the amended claims. The Applicants also cited *In re Angstadt*, 537 F.2d at 502-03, 190 USPQ 214 (CCPA 1976) (deciding that the applicants "are not required to disclose every species encompassed by their claims even in an unpredictable art"). (February 19, 2004 Response at page 41.)

v. August 18, 2004 First Request for Continued Examination (RCE)

As a result of a March 10, 2004 Advisory Action advising the Applicants that the February 19, 2004 Response will not be entered since its amendments raised new issues requiring further search, on August 18, 2004 a first RCE was filed with an amended specification and claims.

vi. October 19, 2004 Non-Final Rejection and April 21, 2005 Amendment



CONFIDENTIAL

November 9, 2015

Page 25

In the October 19, 2004 Non-Final Rejection, the Examiner continued to reject the claims since they have not been amended to the elected group. Claims 1, 38, 39 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for certain heterocyclic groups, did not reasonably provide enablement for any hetero ring from 1-3 atoms of N, O or S. An obviousness double patenting rejection was raised with respect to U.S. Serial Application No. 10/071248. The claims were amended to conform to the elected subject matter and new claims 79-89 were added defining additional embodiments conforming to the elected subject matter.

vii. June 22, 2005 Final Rejection and March 27, 2006 Second RCE

The Examiner continued to maintain the claim rejection for lack of enablement since the claims had still not been amended to the elected group. The Examiner also added a new rejection for lack of written description, both under 35 U.S.C. § 112, first paragraph. Specifically, the Examiner stated that the specification did not have any description or any data to support that the compounds treated cancerous cell growth or that they had an umbrella efficacy to treat any and all cancerous cells. The Examiner also stated that WO 99/32463 cited in another application listed by Applicants in connection with a obviousness double patenting rejection was not prior art for this application.

In response to this final rejection, a second RCE was filed on March 27, 2006 amending the specification to include an in vitro raf kinase assay example indicating that all compounds exemplified displayed IC50s of between 1 nM and 10 μ M. Another example for an in vivo assay of the inhibitory effect of the compounds on tumors (e.g., solid cancers) mediated by raf kinase was also included based on another U.S. application incorporated by reference. The claims were amended to effect a modification of the restriction requirement and to reflect the elected group.

viii. May 25, 2006 Non-Final Rejection and October 30, 2006 Amendment

In a May 25, 2006 Non-Final Office Action the Examiner continued to reject all pending claims. Some claims were rejected (e.g., claims 70 and 72) under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the pharmaceutical composition, did not reasonably provide enablement for the preamble "treatment of a cancerous cell growth." The provisional obviousness double-type patenting rejection over the claims 1-15 of US 10/071248 and those of other applications continued.

In the October 30, 2006 Response, some of the claims were amended to address the rejections under 35 U.S.C. § 112, first and second paragraphs. The Applicants also argued that many of the obviousness double patenting rejections should be withdrawn based on the fact that this was the earlier filed applications.

ix. January 22, 2007 Non-Final Rejection and July 23, 2007 Amendment



CONFIDENTIAL
November 9, 2015
Page 26

In a January 22, 2007 Non-Final Office Action, the Examiner maintained the rejection of claims 70 and 72 under 35 U.S.C. § 112 first paragraph continued. Other claims were also rejected under 35 U.S.C. § 112 first paragraph for lack of enablement. Citing *In re Wands*, the Examiner found that the Applicants failed to provide direction on how to treat all cancers as recited in the claims. Specifically, there were no examples of the compositions used to treat cancerous growth let alone solid tumors, also no examples showing inhibition of the raf kinase enzyme. The rejected claims were directed to pharmaceutical compositions and methods of inhibiting the raf kinase enzyme and they were all dependent upon generic claims. While some of the applications cited under the provisional obviousness-type double patenting rejection were withdrawn, others remained.

In a July 23, 2007 Response, the Applicants cancelled all claims rejected under 35 U.S.C. § 112 first paragraph for lack of enablement. To address the provisional obviousness-type double patenting, the Applicants cancelled relevant claims in these co-pending applications.

x. August 10, 2007 Final Rejection and August 28, 2007 Response

In an August 10, 2007 Final Rejection, the provisional obviousness-type double patenting with respect to many co-pending applications was maintained. In an August 28, 2007 Response, the Applicants provided Terminal Disclaimers with respect to some of the co-pending cited applications and expressly cancelled others in favor of divisional applications.

xi. September 13, 2007 Notice of Allowance

A Notice of Allowance issued on September 13, 2007. No reasons for allowance were provided.

C. Claim Interpretation

All claim terms are given their ordinary, art-recognized meaning.

III. U.S. Patent No. 7,897,623

U.S. Patent Number 7,897,623 (the '623 patent) titled "ω-Carboxyaryl substituted diphenyl ureas as p38 kinase inhibitors" issued March 1, 2011 from application U.S. Serial No. 11/845,597, (the '597 application) filed on August 27, 2007, and claims priority to a parent continuation application, which is U.S. Application Serial No. 10/086,417, filed on March 4, 2002 ('417 application), which is a continuation of U.S. Serial No. 09/425,229 ('229 application) filed on October 22, 1999, which is a continuation-in-part of U.S. Serial No. 09/257,265 ('265 application), filed on February 25, 1999, and claims priority to U.S. Provisional Application No. 60/115,878 ('878 provisional application) filed on January 13, 1999. The inventors named on the face of the patent are Riedl *et al.*

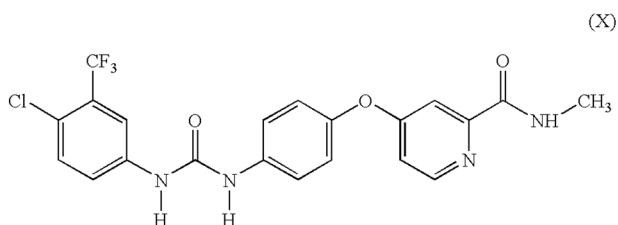
According to the specification, the '623 patent relates to the use of a group of aryl ureas in treating cytokine mediated diseases and proteolytic enzyme mediated diseases, and pharmaceutical compositions for use in such therapy. '623 patent at col. 1, ll. 20-24. Specifically, the '623 patent purports to provide aryl and heteroaryl analogues that inhibit p38 mediated events and thus inhibit the production of cytokines and proteolytic enzymes. *Id.* at col. 2, ll. 35-44. The patent further purports to provide a method of treating protease-mediated diseases in humans or mammals, wherein the protease is one whose production is affected by p38. *Id.* at col. 2, ll. 44-47. Sorafenib (N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea) is disclosed as compound entry no. 42. *Id.* at col. 75-76, Table 4.

As detailed further below, the eight claims of the '623 patent are generally directed to pharmaceutical compositions and tablets comprising compounds, or pharmaceutically acceptable salts thereof. Certain claims further require at least one pharmaceutically acceptable excipient.

A. Claims of the '623 Patent

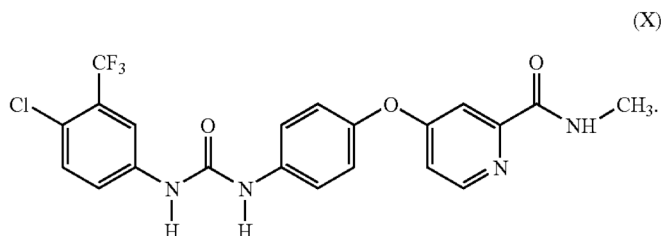
The '623 patent issued with eight claims, or which claims, claims 1, 3, 5 are independent claims. The eight issued claims are reproduced below:

1. A pharmaceutical composition comprising N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula X

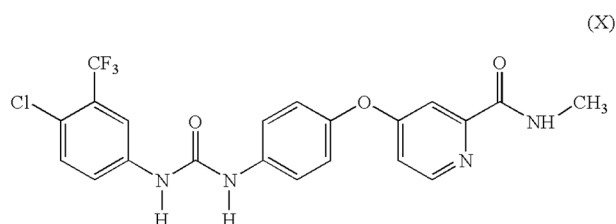


or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

2. The pharmaceutical composition of claim 1 wherein the pharmaceutically acceptable salt thereof is a tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula X

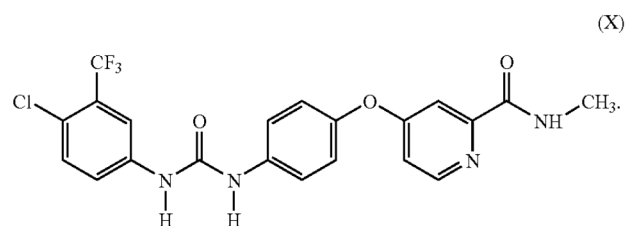


3. A pharmaceutical composition comprising N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula X

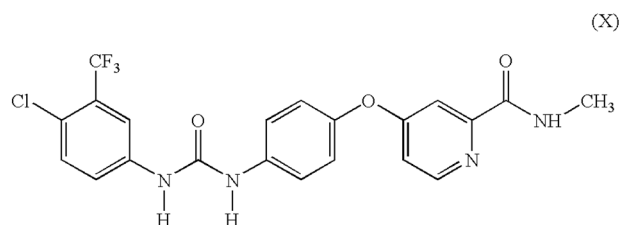


or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier.

4. The pharmaceutical composition of claim 3 wherein the pharmaceutically acceptable salt thereof is a tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula X



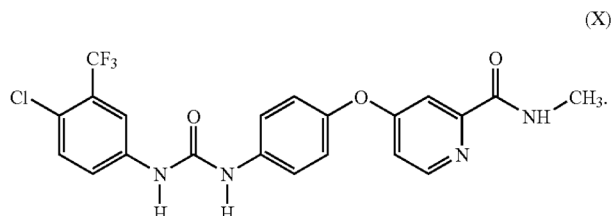
5. A tablet comprising N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula X



or a pharmaceutically acceptable salt thereof, and

at least one pharmaceutically acceptable excipient.

6. A tablet of claim 5 wherein the pharmaceutically acceptable salt thereof is a tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula X



7. A tablet of claim 5 wherein the pharmaceutically acceptable excipient is a diluent, a granulating agent, a disintegrating agent or a binding agent.

8. A tablet of claim 6 wherein the pharmaceutically acceptable excipient is a diluent, a granulating agent, a disintegrating agent or a binding agent.

B. Prosecution History of the '623 Patent

i. Application as Filed

On March 4, 2002, the '417 application was filed as a continuation of the '597 application. The '417 application was filed with 38 original claims directed to methods of treating a disease mediated by p38 by administering a compound reciting sorafenib generically and as a specie. In addition, the claims also recited pharmaceutical compositions for treating a disease within a host mediated by p38 including a compound reciting sorafenib generically and as a specie.

In a March 4, 2002 Preliminary Amendment, the claims directed to pharmaceutical compositions were canceled and additional claims 39-59 directed to methods for treatment of a disease selected from the group of rheumatoid arthritis, rheumatic fever, other inflammatory and infectious diseases were added.

In response to a July 8, 2003 Restriction Requirement, Applicants traversed and elected arthritis as the single disease and sorafenib as the compound embraced by Formula I.

ii. February 10, 2004 Non-Final Office Action and July 31, 2004 Amendment

In the February 10, 2004 Office Action, citing *In re Wands*, the Examiner rejected claims 1, 3, 4, 7-11 under 35 U.S.C. 112, first paragraph as failing to comply with the enablement requirement, because there were no working examples in the specification relating to the



CONFIDENTIAL

November 9, 2015

Page 30

treatment of the claimed diseases. Claims 1, 3, 4, 7-11 were rejected under 35 U.S. C. 103(a) as being unpatentable over U.S. Patent No. 6,093,742 to Salituro *et al.* (Salituro). The Examiner asserted that Salituro disclosed p38 inhibitors useful in the methods for treating inflammation and autoimmune diseases.

In a July 31, 2004 Reply, Applicants amended the claims to recite a “condition” rather than a disease mediated by p38. Applicants provided arguments traversing the lack of enablement and the rejection over Salituro. Regarding Salituro, Applicants argued that while Salituro disclosed urea compounds with bridged cyclic structures, none of these had a substituent on the remote cyclic structure that conforms to L^1 of $A(L(M-L^1)_q$.

iii. November 3, 2004 Final Rejection and February 3, 2005 Response

In this final rejection, the Examiner maintained the rejection of the claims as unpatentable over Salituro. The Examiner stated that while Salituro did not specifically disclose the phenyl groups substituted with the substituents $CON(R_3)_2$, COR_3 and SO_2NR_3 , Salituro did suggest that the aromatic rings may optionally be substituted with these groups. Thus, according to the Examiner, it would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute the phenyl groups of preferred compound 20 and also to reasonably expect that such substitution would not alter the compound’s p38 inhibitory activity, thereby treating patients suffering from rheumatoid arthritis.

In a February 3, 2005 Response, Applicants argued that Salituro did not teach substituting the aromatic rings remotely positioned from the urea group.

iv. October 4, 2005 Request for Continued Examination (RCE), August 4, 2006 Non-Final Rejection and December 8, 2006 Reply

In an August 4, 2006 response to an RCE, a new Examiner maintained the rejection of the claims over Salituro by arguing that there is no restriction in Salituro’s compounds to replace only aromatic rings near the urea group. The Examiner also cited Salituro’s compound 80 where the ring remote to the urea moiety was substituted.

In their December 8, 2006 Reply, Applicants continued to traverse the Salituro rejection by arguing that Salituro’s compound 80 cited by the Examiner did not have a bridging group or cyclic group corresponding to $L1$ and no clear direction to select a substituent for the phenyl moieties corresponding to cyclic structure $L1$.

v. **March 23, 2007 Final Rejection and July 23, 2007 Non-Responsive Amendment**

In response to Applicants' December 8, 2006 Reply, in a March 23, 2007 Final Rejection, the Examiner acknowledged that Applicants' amendment overcame the rejection over Salituro. However, the claims remained provisionally rejected under obviousness-type double patenting over the pending claims of U.S. Application Serial Nos. 09/889,227, 10/071,248, 09/948,915, 10/361,858, 09/993,647, 10/042,203, 10/361,859, 10/308,187 or 10/895,985.

In a July 23, 2007 Non-Responsive Amendment, Applicants cancelled claim 12 to eliminate an obviousness-type double patenting rejection. Applicants also traversed the obviousness-type double patenting rejection with respect to the remaining applications arguing that the claims pending in these applications no longer recite method of treatment claims.

vi. **August 1, 2007 Advisory Action and August 28, 2007 Express Abandonment**

On August 1, 2007, in an Advisory Action, the Examiner maintained the rejection, although he entered the Non-Responsive Amendment and Reply for purposes of appeal. On August 28, 2007, Applicants filed an express abandonment reserving the right to pursue the subject matter in a divisional application.

vii. **August 27, 2007 First Preliminary Amendment, October 10, 2008 Second Preliminary Amendment, September 11, 2009 Third Preliminary Amendment**

On August 27, 2007, Applicants filed the '597 application as a divisional application of the '417 application. In a Preliminary Amendment, Applicants cancelled claims 1-38 and filed claims 39-55. All claims were directed to a method of treating a condition mediated by p38 by administering to a host a compound of Formula I, A-D-B, wherein D is -NH-C(O)-NH-, A is a substituted moiety of up to 40 carbons atoms of the formula -L-M-L¹)_q and B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety and L¹ is substituted by at least one substituent selected from the group consisting of -SO₂R_x, -C(O)R_x and -C(NR_y) R_z. In these claims, L¹ did not recite pyridyl and B was not phenyl. The elected disease was arthritis and the specie was N-(5-tert-butyl-2-methoxyphenyl)-N'-(4-(-methoxy-3-(N-methylcarbamoyl)phenoxy)phenyl)urea, which is not sorafenib. This was done to avoid an obviousness-type double patenting rejection in copending application U.S. Serial No. 09/889,227, which subsequently issued as U.S. Patent No. 7,351,834.

In a second Preliminary Amendment, Claims 39, 40 and 42 were cancelled and other claims were amended to eliminate from the claims all compounds of formula I wherein either L1 was pyridyl or B was phenyl.

Finally, in a third Preliminary Amendment, all pending claims directed to methods of treatment were cancelled and new claims 56-63 directed to pharmaceutical compositions were added. Compound 42 of the specification conformed to formula X, which recites sorafenib.

viii. December 7, Notice of Allowance, December 23, 2009 RCE and January 4, 2010/February 8, 2010 Notices of Allowance

In a December 7, Notice of Allowance issued in response to the previously filed Preliminary Amendments, the Examiner allowed the application after having conducted a structure search and finding no reference that would anticipate or render obvious the claimed compositions. The Examiner further stated that the claims were in compliance with §§ 112, first and second paragraphs. Accordingly, claims 56-63 (all claims) were allowed.

In a December 23, 2009 RCE, Applicants reopened the prosecution of this application by filing an Information Disclosure Statement (IDS) listing U.S. applications relating to aryl ureas as kinase inhibitors. On January 4, 2010 and February 8, 2010, in response to the IDS previously filed, two identical Notices of Allowance followed indicating that claims 56-63, directed to pharmaceutical compositions remained in condition for allowance.

ix. April 29, 2010 RCE/Change in Inventorship, June 3, 2010 Non-Final Quayle Office Action and July 30, 2010 Response

The Preliminary Amendment filed on September 11, 2009, necessitated a change in inventorship. An April 29, 2010 RCE was filed to implement this change. In response, the Examiner issued an Ex parte Quayle Office Action requesting proper renumbering of the pending claims.

In a July 30, 2010 Response to the Quayle Office Action, Applicants requested a corrected filing receipt and refiled claims 56-63 indicating that all previous claims had been deleted.

x. September 15, 2010 Notice of Allowance, November 1, 2010 Amendment After Final

A Notice of Allowance followed without any reason for allowability, where the same claims as previously allowed remained allowed. In a November 1, 2010 Amendment After Final, Applicants identified this application as a continuation application rather than as a divisional application.

xi. Terminal Disclaimers

On March 10, 2011 terminal disclaimers were filed with respect to U.S. Patent No. 7,235,576 and U.S. Patent No. 7,351,834. These Terminal Disclaimers were resubmitted on May 10, 2011 since they had to be resubmitted with a copy of the power of attorney. The refiled



CONFIDENTIAL
November 9, 2015
Page 33

terminal disclaimers were again disapproved. Nevertheless, the '623 patent issued on March 1, 2011.

C. Claim Interpretation

All claim terms are given their ordinary and art-recognized meaning. None of the claims of the '623 patent recite any diseases or conditions being treated by these pharmaceutical compositions or tablets.

IV. U.S. Patent No. 7,235,576

U.S. Patent No. 7,235,576 ('576 patent) entitled "ω-Carboxyaryl substituted diphenyl ureas as raf kinase inhibitors" issued June 26, 2007, from application U.S. Serial No. 10/042,203 (the '203 application) filed on January 11, 2002, and claims priority from U.S. Provisional Application No. 60/367,380 ('380 provisional application) filed on January 12, 2001. The inventors named on the face of the patent are Riedl *et al.*

The '576 patent relates to the use of aryl ureas in treating raf mediated diseases, and pharmaceutical compositions for use in such therapy. '576 patent at col. 1, ll. 9-11. The '576 patent specifically purports to disclose inhibitors of the enzyme raf kinase, which would be used in pharmaceutical compositions for human or veterinary use, including treatment of tumors and/or cancerous cell growth mediated by raf kinase. *Id.* at col. 1, ll. 49-55. In particular, these compounds purport to be useful in the treatment of human or animal solid cancers. *Id.* at col. 1, ll. 55-65.

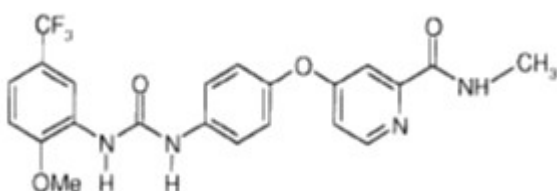
The seventeen claims of the '576 patent are generally directed to pharmaceutically acceptable salts of certain compounds.

A. Claims of the '576 Patent

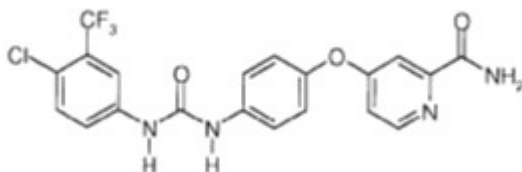
The '576 patent issued with forty-seven claims. Claims 2-47 were thereafter replaced by claims 2-17 as detailed in the Certificate of Correction on February 24, 2009. Of the seventeen claims, claims 1, 4, 5, 7, 8, 10, 11, 13, 14, 16 are independent. Claims 1-17 are reproduced below:

1. A pharmaceutically acceptable salt of a compound selected from the group consisting of:
N-(5-tert-butyl-2-methoxy phenyl)-N'-(4-(4-methoxy-3-(N-methylcarbamoyl)phenoxy)phenyl)urea,
N-(2-methoxy-5-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl-4-pyridyloxy)phenyl)urea,
N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-carbamoyl-4-pyridyloxy)phenyl)urea,
N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea;
N-(2-methoxy-4-chloro-5-(trifluoromethyl)phenyl)-N'-(3-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea and their pharmaceutically acceptable salts.
2. A pharmaceutically acceptable salt of claim 1, which is
 - a) a basic salt of an organic acid or an inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-napthalene sulfonic acid, 2-napthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid,

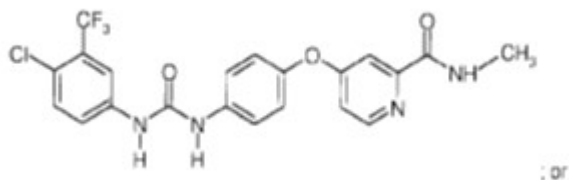
- lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid; or
- b) an acid salt of an organic or inorganic base containing an alkali metal cation, an alkaline earth metal cation, an ammonium cation, an aliphatic substituted ammonium cation or an aromatic substituted ammonium cation.
3. A pharmaceutically acceptable salt of claim 1 which is a basic salt of an organic acid or an inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid.
4. A pharmaceutically acceptable salt which is the tosylate salt of
N-(5-*tert*-butyl-2-methoxy phenyl)-*N'*-(4-(4-methoxy-3-(*N*-methylcarbamoyl) phenoxy) phenyl) urea,
N-(2-methoxy-5-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea,
N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea,
N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea; or
N-(2-methoxy-4-chloro-5-(trifluoromethyl) phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea.
5. A pharmaceutically acceptable salt of a compound which is:
N-(2-methoxy-5-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



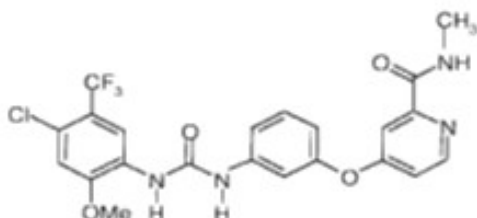
N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



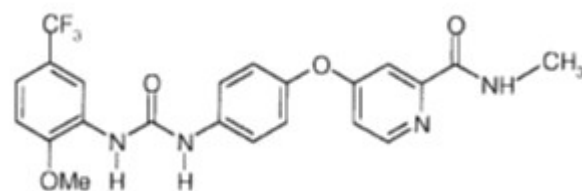
N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



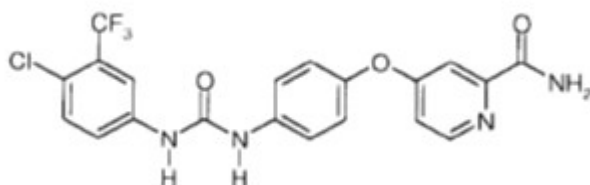
N-(2-methoxy-4-chloro-5-(trifluoromethyl) phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



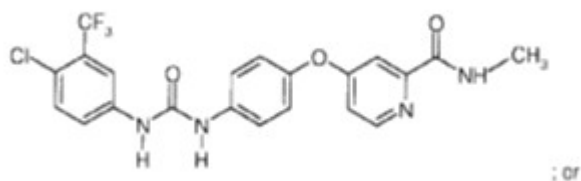
6. A pharmaceutically acceptable salt of claim 5 which is a basic salt of an organic acid or an inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylactic acid, or mandelic acid.
7. A pharmaceutically acceptable salt which is the tosylate salt of *N*-(2-methoxy-5-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



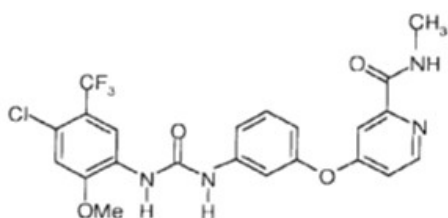
N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-carbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:

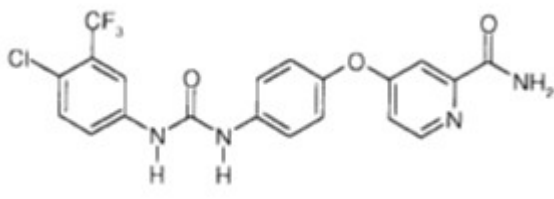


N-(2-methoxy-4-chloro-5-(trifluoromethyl) phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:

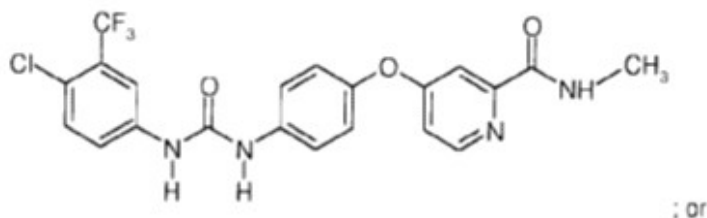


8. A pharmaceutically acceptable salt of a compound which is:

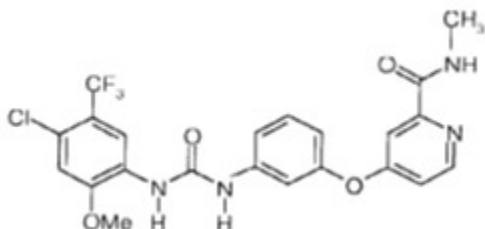
N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-carbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



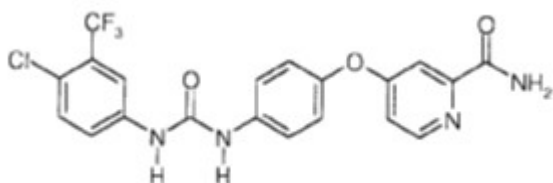
N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



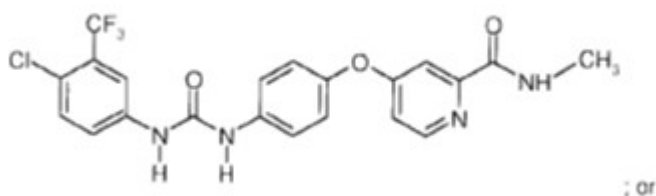
N-(2-methoxy-4-chloro-5-(trifluoromethyl) phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



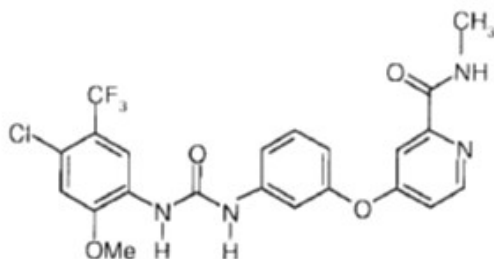
9. A pharmaceutically acceptable salt of claim 8 which is a basic salt of an organic acid or an inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylactic acid, or mandelic acid.
10. A pharmaceutically acceptable salt which is the tosylate salt of
N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-carbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



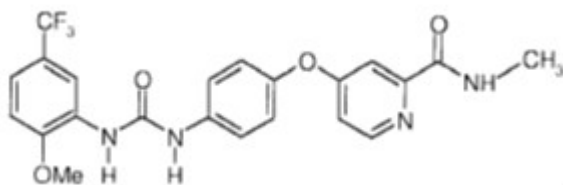
N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



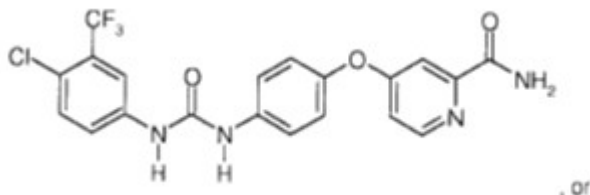
N-(2-methoxy-4-chloro-5-(trifluoromethyl) phenyl)-*N'*-(3-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



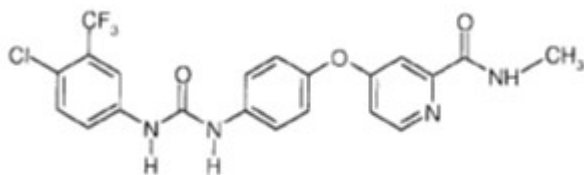
11. A pharmaceutically acceptable salt of a compound which is:
N-(2-methoxy-5-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:

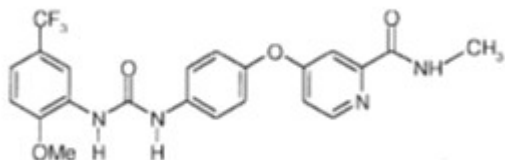


N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:

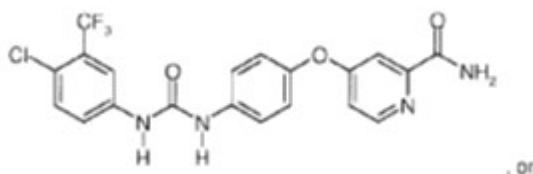


12. A pharmaceutically acceptable salt of claim 8 which is a basic salt of an organic acid or an inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylactic acid, or mandelic acid.

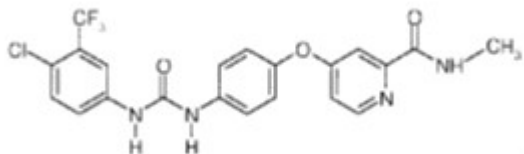
13. A pharmaceutically acceptable salt which is the tosylate salt of *N*-(2-methoxy-5-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



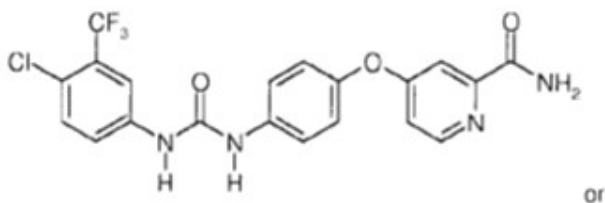
N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-carbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



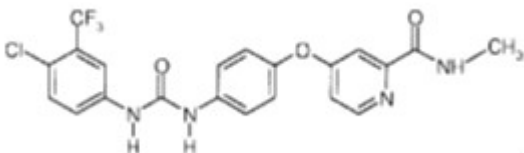
N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



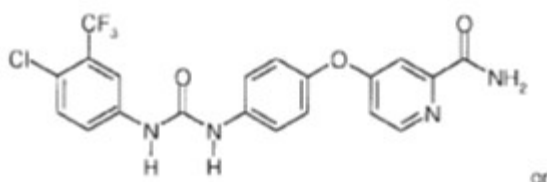
14. A pharmaceutically acceptable salt of a compound which is: *N*-(2-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-carbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:

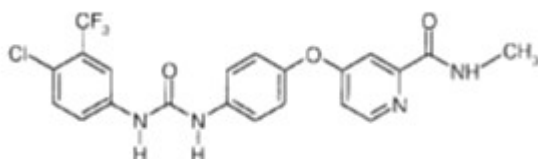


15. A pharmaceutically acceptable salt of claim 14 which is a basic salt of an organic acid or an inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylactic acid, or mandelic acid.
16. A pharmaceutically acceptable salt which is the tosylate salt of
N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-carbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



or

N-(4-chloro-3-(trifluoromethyl) phenyl)-*N'*-(4-(2-(*N*-methylcarbamoyl)-4-pyridyloxy) phenyl) urea of the formula:



17. A pharmaceutical composition comprising a pharmaceutically acceptable salt of claim 1, 2, 3, 4, 5, 6, 7, 8,9,10, 11, 12,13,14,15 or 16 and pharmaceutically acceptable carrier.

B. Prosecution History of the '576 Patent

i. Application as Filed

On January 11, 2002, the '203 application was filed claiming priority to provisional application no. 60/367,380 filed on January 12, 2001. The '203 application was filed with 67 original claims directed to pharmaceutically acceptable salts, including sorafenib. In a January 11, 2002 Preliminary Amendment, claims 1-49, 61-65, and 67 were cancelled, and new claims 68-109 were added. New claims were directed to a pharmaceutically acceptable salts, including sorafenib. In addition, the claims also recited a method for the treatment of a cancerous cell growth mediated by raf kinase comprising administering a pharmaceutically acceptable salt of a compound selected from the group consisting of sorafenib, or other non-sorafenib compounds. On June 7, 2002, an IDS was filed.



CONFIDENTIAL

November 9, 2015

Page 42

ii. July 30, 2002 Notice of Allowance

In a July 30, 2002 Notice of Allowance, claims 68-109 were allowed. In the Reasons for allowance, the Examiner cited U.S. Patent No. 5,470,882 (Dixon *et al*), U.S. Patent No. 5,447,957 (Adams *et al*), EP Application No. 0379915 (Busse *et al*) and WO 99/32463 (Miller *et al*). The Examiner stated that the references did not disclose either a carbamoyl group or a carbamoyl substituent.

iii. November 19, 2002 Amendment and IDS

On October 30, 2002, an RCE was filed to withdraw the application from allowance so that on November 19, 2002, an Amendment and an IDS could be filed. The amendments to the specification and claims were mainly typographical changes.

iv. January 23, 2003 Non-Final Office Action

In a January 23, 2003 non final Office Action, claims 50-54, 68-73, and 105-109 were rejected under 35 U.S.C. § 103 for being obvious over U.S. Patent No. 5,447,957 (Adams). Claims 50-54 and 68-109 were rejected for "same invention" double patenting under 35 U.S.C § 101 over co-pending application nos. 10/071,248, 09/773,604, 09/773,659, 09/773,658, 09/773,672, 09/773,675, 09/755,060, 08/863,022, 09/947,761 and 09/776,936.

v. June 26, 2003 Response to Office Action and August 13, 2003 Notice of Allowance

In a June 26, 2003 response, Applicants argued against the § 103 rejection without amending the claims. With regard to the double patenting rejections, Applicants argued that the claimed compounds of the co-pending applications were structurally distinct from the compounds claimed. Applicants also advised the Examiner that 09/773,604, 09/773,675, 09/773,659, 09/773,658, and 09/773,672 had been abandoned. On August 13, 2003, a Notice of Allowance issued wherein the Examiner stated that the references in the IDS could not be considered since they did not include a publication date.

vi. November 13, 2003 RCE and IDS

On November 13, 2003, an RCE was filed to remove the application from allowance, and to file a complying IDS.

vii. January 27, 2004 Non Final Office Action and July 27, 2004 Response

In a January 27, 2004 Office Action, the Examiner rejected claim 74 under 35 U.S.C. § 112 for indefiniteness, but allowed claims 50-54 and 68-100. In a July 27, 2004 Amendment, Applicants argued against the § 112 rejection, filed another IDS and added claims 110-124. The

amendment was found to be Non-Compliant as Applicants failed to list all cancelled claims. Applicants' compliant Amendment was filed on September 3, 2004.

viii. November 12, 2004 Final Office Action and May 16, 2005 Amendment

In a November 12, 2004 Office Action, the Examiner maintained the 35 U.S.C. § 112 indefiniteness rejection of claim 74 and claims 50-54 and 68-100 were still found to have allowable subject matter. A May 16, 2005 Amendment adding claims 125-136, which correspond to issued claims 5-16 was filed together with another RCE.

ix. July 26, 2005 Non-Final Office Action and October 28, 2005 Amendment

In a July 26, 2005 Office Action, the pending claims were rejected for obviousness double patenting over co-pending application nos. 09/889,227, 10/361,858, 10/895,985, 10/848,567, and 10/071,248. In an October 28, 2005 response, Applicants argued against the double patenting rejections without filing terminal disclaimers. An IDS was submitted concurrently with the Amendment.

x. January 23, 2006 Non-Final Office Action

In a January 23, 2006 Office Action, the Examiner maintained the previous double patenting rejections. The Examiner also rejected the claims under 35 U.S.C. § 102(e) in view of the co-pending applications cited in the double patenting rejections. The Examiner alleged that the cited references taught the carbamoyl derivatives recited in the current claims.

xi. July 24, 2006 Response and Inventor Declarations under 37 CFR 1.131

On July 24, 2006, a response was filed with 1.131 Declarations. In the Declarations, the inventors asserted that the references in the 102(e) rejections had a priority date of January 13, 1999; however, the claimed compounds were invented at least as early as January 13, 1999. The Inventors requested that the 102(e) rejections be withdrawn in view of Applicants' date of alleged invention.

xii. October 13, 2006 Examiner Interview and Preliminary Amendment

In an October 13, 2006 Examiner Interview, the Examiner requested the status of Application No. 09/758,847. In the Examiner Interview and further clarified in an October 13, 2006 preliminary amendment, Application No. 09/758,847 was found to have been converted to provisional application no. 60/367,380, the provisional application to which the '203 application claims priority.

xiii. January 12, 2007 Notice of Allowance



CONFIDENTIAL
November 9, 2015
Page 44

In a January 12, 2007 Notice of Allowance, the Examiner stated that the declarations submitted on July 24, 2006 overcame the 102(e) rejection. Further, the double patenting rejections were withdrawn.

xiv. March 2, 2007 Amendment Under 1.312

On March 2, 2007, an Amendment under 1.312 was submitted to correct certain informalities in the claims.

xv. August 21, 2007 and February 24, 2009 Certificate of Corrections

On August 21, 2007 and February 24, 2009, Certificates of Correction were issued after requests were submitted.

xvi. March 23, 2004 and August 13, 2009 Terminal Disclaimers

On March 23, 2004 and August 13, 2009, terminal disclaimers were filed with respect to U.S. Patent Application No. 09/993,647 and U.S. Patent No. 7,351,834 (previously U.S. Patent Application No. 09/889,227). The '576 patent issued on June 26, 2007.

C. Claim Interpretation

All claim terms are given their ordinary, art-recognized meaning.

V. U.S. Patent No. 8,841,330

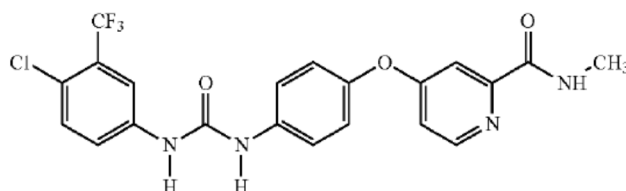
The '330 patent is entitled "Omega-Carboxyaryl Substituted Diphenyl Ureas As Raf Kinase Inhibitors." The '330 patent issued on September 23, 2014, from U.S. patent application serial no. 13/368,812, filed on February 8, 2012 as a continuation of application no. 09/993,647, filed on November 27, 2001 (now U.S. patent no. 8,124,630), and claiming priority to provisional application no. 60/367,346, filed on November 28, 2000.

Thus, the earliest possible effective U.S. filing date and the earliest possible priority date for the '330 patent is November 28, 2000. Pursuant to a terminal disclaimer, the '330 patent is projected to expire on January 12, 2020.

A. Claims of the '330 Patent

The claims of the '330 patent are each directed to a method of treating a tumor or cancer of the prostate, breast, liver, ovary, or cervix by administering sorafenib. The claims are:

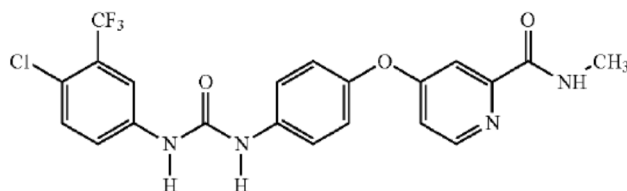
1. A method for the treatment of a tumor of the prostate, breast, liver, ovary or cervix in a human or animal comprising administering an effective amount of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula:



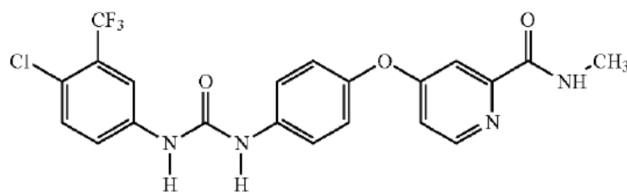
or a pharmaceutically acceptable salt thereof.

2. A method as in claim 1 wherein the tumor is of the prostate.
3. A method of claim 1 wherein the tumor is of the breast.
4. A method of claim 1 wherein the tumor is of the liver.
5. A method of claim 1 wherein the tumor is of the ovary.
6. A method of claim 1 wherein the tumor is of the cervix.
7. A method for the treatment of a tumor of the prostate, breast, liver, ovary or cervix in a human or animal comprising administering an effective amount of a tosylate

salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula:

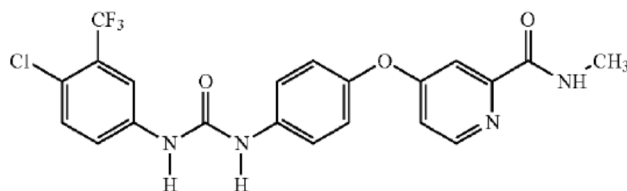


8. A method as in claim 7 wherein the tumor is of the prostate.
9. A method of claim 7 wherein the tumor is of the breast.
10. A method of claim 7 wherein the tumor is of the liver.
11. A method of claim 7 wherein the tumor is of the ovary.
12. A method of claim 7 wherein the tumor is of the cervix.
13. A method for the treatment of liver cancer in a human or animal in need thereof comprising administering an effective amount of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula:



or a pharmaceutically acceptable salt thereof.

14. A method of claim 13 wherein a tosylate salt of N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea of the formula:





CONFIDENTIAL
November 9, 2015
Page 47

is administered.

B. Prosecution History of the '330 Patent

During prosecution of the '330 patent, the examiner found written description support for the claims based on the specification's recitation that "the compounds of the invention are useful in treating cancers, including solid cancers" (col.1 ll.65-67) and based on several references provided by the applicant that purportedly recite the types of solid cancers recited in the claims. Office Action 8-9 (Nov. 8, 2013).

Also during prosecution, the applicant successfully argued that an obviousness-type double patenting rejection based on parent U.S. patent no. 8,124,630 ("the '630 patent") did not apply. Specifically, the applicant stated:

The pending claims are directed to treating tumors of the prostate, breast, liver, ovary or cervix whereas claim [sic] 1-16 of US Patent No. 8,124,630 are directed to treating carcinoma of the lung, pancreas, thyroid, bladder or colon. The treatment methods claimed are directed to distinct cancers and are not obvious variants of the methods defined in claims 1-16 of US Patent No. 8,124,630.

Response to Office Action 5 (Feb. 10, 2014).

C. Claim Interpretation

All claim terms are given their ordinary, art-recognized meaning.

VI. U.S. Patent No. 8,877,933

The '933 patent issued from application no. 11/664,363, which has a 35 U.S.C. § 371(c) date of June 20, 2008 and is a national stage application of international application no. PCT/EP2005/010119 filed September 20, 2005, which in turn claims priority to European application no. 04023130.0 filed September 29, 2004.⁴ Thus, the critical date for prior art to qualify as prior art to the '933 patent under 35 U.S.C. § 102(b) is September 20, 2004. The '933 patent is expected to expire on September 20, 2025, not including any patent term adjustment or patent term extension that may be applied.

The '933 patent is directed generally to polymorphic forms of sorafenib tosylate, methods of their preparation, and pharmaceutical compositions containing polymorphic form I. According to the specification, Two polymorphic forms of sorafenib tosylate are discussed in the '933 patent. Form I of sorafenib tosylate is thermodynamically stable at room temperature and is stable in storage, even when processing via suspensions. '933 patent, col.2, ll.30-37.

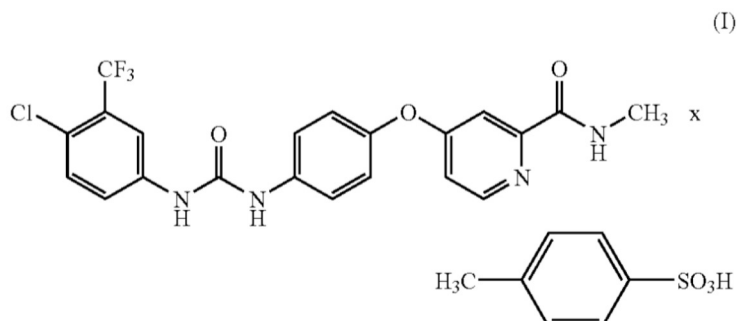
According to the '933 patent, form II of sorafenib tosylate is formed via the methods disclosed in WO 00/42012, replicated as Example 1 of the '933 patent. *Id.* at col.2, ll.12-16; col.13, ll.35-52. Form II is metastable and has a conversion point of 194°C, at which Form II converts to Form I. *Id.* at col.2, ll.51-54. The '933 patent discloses several manners of producing Form I that begin with Form II. The first disclosed method is to place Form II in an inert solvent, heat the mixture to reflux, cool the mixture, and isolate crystals of polymorphic Form I therefrom. *Id.* at col.12, ll.10-25. The '933 patent also discloses a method for the preparation of polymorphic Form I, where Form II is placed in an inert solvent, heated to reflux, seeded with polymorphic Form I, and stirred or shaken at room temperature for approximately one hour to fourteen days. Crystals of polymorphic Form I are thus formed. *Id.* at col.12, ll.26-39.

The '933 patent further discloses a method where sorafenib tosylate Form II is placed in an inert solvent at room temperature until it is converted into sorafenib tosylate Form I. The conversion occurs with or without seeding with crystals of Form I. *Id.* at col.11, ll.48-59. The '933 patent further discloses a method where sorafenib tosylate Form II is heated from 195 to 222°C at a heating rate of 10 to 30°C/min., and subsequently cooled to room temperature (10-30°C) at a cooling rate of 1°C to about 4°C/min. *Id.* at col.12, ll.54-62.

A. Claims of the '933 Patent

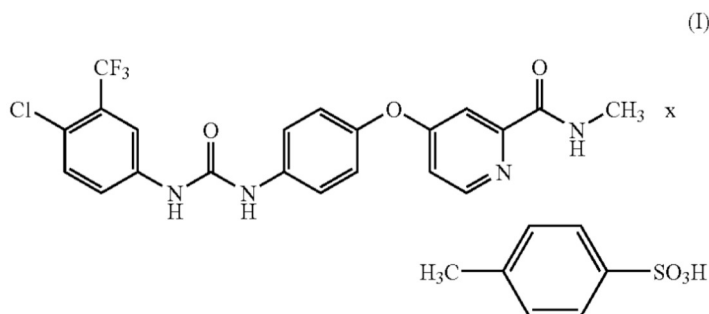
The following are the claims of the '933 patent:

1. A compound of the formula (I)



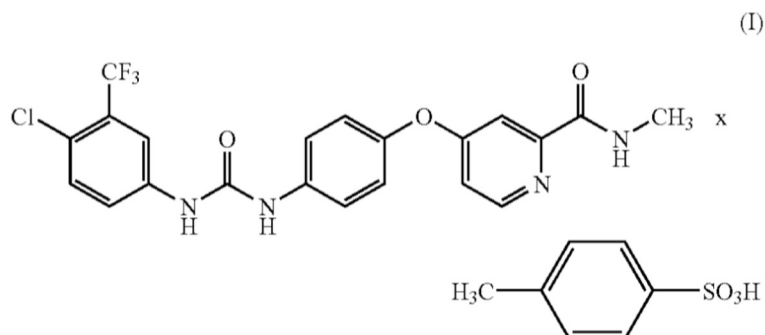
in the polymorph I form, which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5.

2. The compound of claim 1 which shows in the X-ray diffractometry peak maxima of the 2 theta angle comprising 4.4, 14.8, 20.5, 20.8, 21.5 and 22.9.
3. The compound of claim 1 which shows in the IR spectrum a peak maximum of 1724 cm⁻¹.
4. The compound of claim 1 which shows in the Raman spectrum a peak maximum of 1723 cm⁻¹.
5. A method of preparing the compound of formula (I)



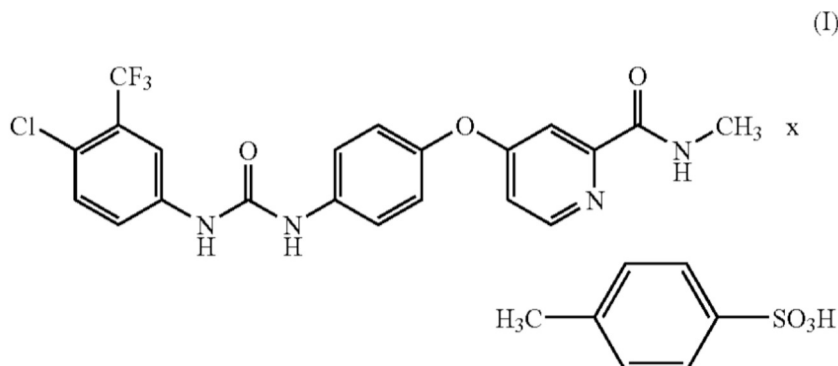
in the polymorph I form which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5, comprising contacting a compound of formula (I) in the polymorph II form with an inert solvent under conditions sufficient to quantitatively convert the compound in the polymorph II form to the polymorph I form.

6. The method according to claim 5, further comprising the step of seeding the inert solvent with crystals of a compound of the formula (I) in the polymorph I form.
7. A method of preparing a compound of formula (I)



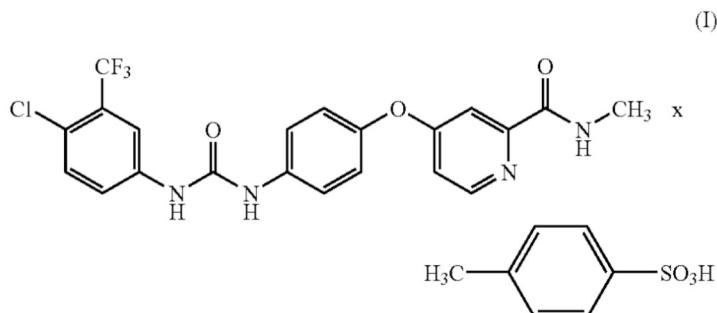
in the polymorph I form which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5, comprising heating a compound of formula (I) in the polymorph II form from 195°C. to 222°C. at a heating rate of 10°C. to 30°C. per minute and subsequently cooling to 10°C. to 30°C. at a cooling rate of from 1 to 4°C. per minute.

8. A pharmaceutical composition comprising a compound of formula (I):



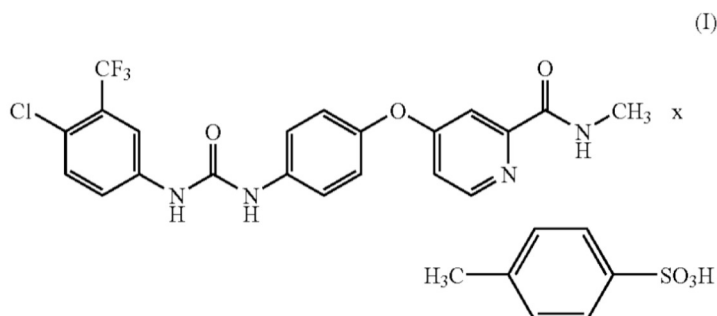
substantially in the polymorph I form which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5.

9. The pharmaceutical composition as claimed in claim 8, further comprising one or more inert, nontoxic, pharmaceutically suitable excipients.
10. The pharmaceutical composition of claim 8, wherein the compound of formula (I) is present in the polymorph I form in the composition in an amount equal to or more than 90 percent by weight of the total weight of the compound of formula (I) present in the composition.
11. The pharmaceutical composition according to claim 8, further comprising another pharmaceutical agent where the combination causes no unacceptable side effects.
12. The pharmaceutical composition of claim 8, further comprising another pharmaceutical agent which is a cytotoxic agent, a signal transduction inhibitor, an anti-cancer agent, or an antiemetic.
13. A pharmaceutical composition comprising a compound of formula (I):



substantially in the polymorph I form which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5, and at least one additional pharmaceutical agent.

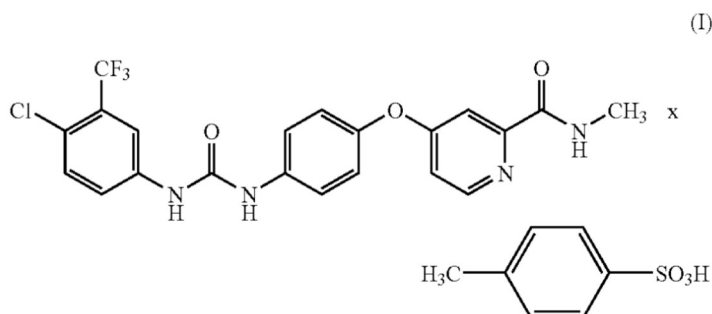
14. The pharmaceutical composition of claim 13, further comprising one or more inert, nontoxic, pharmaceutically suitable excipients.
15. The pharmaceutical composition of claim 13, wherein said additional pharmaceutical agent is a cytotoxic agent, a signal transduction inhibitor, an anti-cancer agent, or an antiemetic.
16. A method of treating a disorder, comprising administering to a subject in need thereof a therapeutically effective amount of a compound of formula (I)



in the polymorph I form which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5.

17. The method of claim 16, wherein the disorder is selected from the group consisting of abnormal angiogenesis, hyperpermeability processes, bone marrow diseases, carcinoma and carcinogenic cell growth.
18. The method of claim 16, wherein the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid gland, kidney or intestine.
19. A method for treating a disorder, comprising administering to a subject in need thereof a therapeutically effective amount of the pharmaceutical composition of any one of claims 8 to 15.

20. The method of claim 19, wherein the disorder is selected from the group consisting of abnormal angiogenesis, hyperpermeability processes, bone marrow diseases, carcinoma and carcinogenic cell growth.
21. The method of claim 19, wherein the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid gland, kidney or intestine.
22. A method of preparing a compound of formula (I)



- in the polymorph I form which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5, comprising dissolving or suspending a compound of formula (I) in the polymorph II form in an inert solvent and stirring or shaking under conditions sufficient to quantitatively convert the compound in the polymorph II form to the polymorph I form.
23. The compound of the formula (I) as claimed in claim 22, wherein the process for its preparation further comprises the step of seeding the inert solvent with crystals of a compound of the formula (I) in the polymorph I form.
 24. The compound of claim 1 prepared by dissolving or suspending a compound of formula (I) in the polymorph II form in an inert solvent and stirring or shaking under conditions sufficient to quantitatively convert the compound in the polymorph II form to the polymorph I form.
 25. The compound of claim 1 prepared by dissolving or suspending a compound of formula (I) in the polymorph II form in an inert solvent, seeding the inert solvent with crystals of a compound of the formula (I) in the polymorph I form and stirring or shaking under conditions sufficient to quantitatively convert the compound in the polymorph II form to the polymorph I form.
 26. The compound of claim 1 prepared by a method comprising heating a compound of formula (I) in the polymorph II form from 195°C to 222°C at a heating rate of 10°C to 30°C per minute and subsequently cooling to 10°C to 30°C at a cooling rate of from 1 to 4°C per minute to quantitatively convert the compound in the polymorph II form to the polymorph I form.
 27. The compound of claim 1 which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5, which shows in the IR spectrum a peak maximum of 1724 cm⁻¹ and which shows in the Raman spectrum a peak maximum of 1723 cm⁻¹.
 28. A compound having the x-ray diffraction pattern of polymorph I in FIG. 2 of the application which shows in the X-ray diffractometry peak maxima of the 2 theta angle of 4.4, 14.8 and 20.5.

29. The compound of claim 1 which shows in the X-ray diffractometry peak maxima of the 2 theta angle comprising: 4.4, 13.2, 14.8, 16.7, 17.9, 20.1, 20.5, 20.8, 21.5 and 22.9.
30. The compound of claim 1 which shows in the X-ray diffractometry peak maxima of the 2 theta angle comprising: 4.4, 10.7, 11.1, 11.4, 11.6, 12.2, 12.8, 13.2, 14.8, 16.5, 16.7, 17.7, 17.9, 18.8, 19.3, 19.6, 20.1, 20.5, 20.8, 21.5, 21.7, 22.3, 22.5, 22.9, 23.4, 23.7, 24.0, 24.5, 25.1, 25.4, 26.0, 26.4, 26.6, 27.0, 27.6, 28.2, 28.6, 28.8, 29.3, 29.6, 29.9, 30.8, 31.2, 31.6, 31.8, 32.1, 32.4, 32.7, 33.1, 33.8, 34.2, 34.6, 35.4, 35.7 and 37.1.
31. The compound of claim 1 which melts under decomposition at 223°C.-231°C.

B. Prosecution History of the '933 Patent

The USPTO repeatedly rejected the pending claims that recited polymorphic Form I of sorafenib tosylate over Dumas PCT application no. WO 03/068228 ("Dumas") and over the combination of Dumas in further view of Sidransky (U.S. patent application publication no. 2005/0048533; "Sidransky"), as applied to certain dependent claims. In making those rejections, the Examiner argued that all polymorphic forms of sorafenib are inherently contained upon formation of the crystalline form disclosed in Dumas. In light of that, the Examiner took the position that it would have been obvious that Form I would display the x-ray diffraction (XRD), infrared (IR), and Raman spectra characteristics claimed by the applicants. Office Action, May 26, 2010. The Examiner also argued that any unexpected properties of the Form I polymorph are not persuasive indications of non-obviousness because they were inherent in the crystalline forms of sorafenib tosylate that were already disclosed.

In response, the Applicants argued that sorafenib tosylate Form I was both novel and non-obvious. The Applicants pointed out that Dumas prepared the free base, not the tosylate salt, and that references that do disclose a tosylate salt (e.g., PCT application no. WO03/047579 to Carter ("the '579 publication") and PCT application no. WO00/042012 to Riedl et al. ("the '012 publication")) do not disclose or suggest the claimed polymorphic form. *See, e.g.*, Response, Oct. 21, 2011 at 11-12. In arguing against the obviousness rejections issued by the USPTO, the Applicants argued that "[n]o art has been cited to show the methods for preparing the claimed polymorph I were known or predictable. Furthermore, no art has been cited to show there was any advantage or motivation to identify other crystal structure (polymorphs)." July 25, 2012 Response at 12.

The Examiner and Applicants essentially maintained these positions throughout the prosecution, with the Examiner finally relenting and issuing of a notice of allowance on September 17, 2012. This was the first of six notices of allowance issued by the USPTO for this application. The pending claims remained unchanged during the filing of multiple requests for continuing examination, though numerous references were submitted for consideration by the Applicants. The sixth and final notice of allowance was issued on June 26, 2014, and the Applicants paid the issue fee on September 26, 2014. The '933 patent issued on November 4, 2014.



CONFIDENTIAL
November 9, 2015
Page 54

C. Claim Interpretation

All claim terms are given their ordinary, art-recognized meaning Claims 1-4 are directed to the polymorphic form I of sorafenib tosylate. Claims 5-7 and claims 22-23 relate to methods of preparation of polymorphic form I of sorafenib tosylate. Claims 8-15 are directed to pharmaceutical compositions that include form I of sorafenib tosylate. Claims 16-21 recite methods of treating a disorder with form I of sorafenib tosylate, with claim 17 limiting the disorder to abnormal angiogenesis, hyperpermeability processes, bone marrow diseases, carcinoma, or carcinogenic cell growth.

VII. Noninfringement Analysis

A. U.S. Patent No. 7,351,834

Mylan's sorafenib tosylate tablets, 200 mg, would not infringe claims 3, 6-18, 20-23, 26, 27, 33, and 34 either literally or under the doctrine of equivalents.

Claims 3, 6-18¹, 20-23, 26, 27, 33 and 34 would not be infringed by Mylan's sorafenib tosylate tablets. These claims do not recite sorafenib and/or sorafenib tosylate. Since Mylan does not plan to include any other active compounds in its proposed sorafenib formulations, any proposed Mylan sorafenib formulation which does not include another active ingredient encompassed by these claims cannot literally infringe these claims of the '834 patent.

Moreover, claims 3, 6-18, 20-23, 26, 27, 33 and 34 could not be infringed also under the doctrine of equivalents because these claims do not recite a compound that is equivalent to sorafenib.

B. U.S. Patent No. 8,841,330

Mylan's ANDA for Mylan's Proposed Sorafenib Tosylate Product does not infringe claims 2, 3, 5, 6, 8, 9, 11, or 12 of the '330 patent because Mylan's ANDA does not seek approval to use sorafenib tosylate for the methods of those claims. Specifically, Mylan's ANDA seeks approval to use sorafenib tosylate for the treatment of unresectable hepatocellular carcinoma and advanced renal cell carcinoma. Because Mylan's ANDA does not seek approval to use sorafenib to treat tumors of the prostate, breast, ovary, or cervix, Mylan's ANDA does not literally infringe claims 2, 3, 5, 6, 8, 9, 11, or 12 of the '330 patent. *See Bayer*, 676 F.3d at 1321-22.

Mylan's ANDA also does not infringe any of those claims under the doctrine of equivalents because a finding that a tumor of the prostate, breast, ovary, or cervix is equivalent to unresectable hepatocellular carcinoma or advanced renal cell carcinoma would vitiate the applicable claim limitations. *See Carnegie Mellon Univ. v. Hoffmann-La Roche Inc.*, 541 F.3d 1115, 1129 (Fed. Cir. 2008) ("In determining whether a finding of infringement under the doctrine of equivalents would vitiate a claim limitation, we must consider 'the totality of the circumstances of each case and determine whether the alleged equivalent can be fairly characterized as an insubstantial change from the claimed subject matter without rendering the pertinent limitation meaningless.'" (quoting *Freedman Seating Co. v. Am. Seating Co.*, 420 F.3d 1350, 1359 (Fed. Cir. 2005))).

¹ Claims 7, 8 and 33 and their dependent claims 11 and 12, respectively, recite "optional" or "optionally" language, which has been interpreted as requiring the presence of at least one of the cited groups. Otherwise, the claims would recite sorafenib, which would be invalid for reasons explained in Section IX.A.

C. U.S. Patent No. 8,877,933

Claims 5-7, 11-15, and 22-26 of the '933 patent would not be infringed by Mylan's Proposed Sorafenib Product. Claims 5-7 and 22-26 of the '933 patent each recite a method of making sorafenib tosylate form I that converts form II into form I. Specifically, those methods include contacting sorafenib tosylate form II with an inert solution to convert the same into sorafenib tosylate form I (claim 5 and 6), heating form II and cooling the resultant composition (claims 7 and 26), or dissolving or suspending sorafenib tosylate form II in an inert solvent and stirring or shaking it to convert the same into sorafenib tosylate form I (claims 22-25). Natco's process only synthesizes sorafenib tosylate form I. Natco, therefore, does not convert form II to form I, as required by claims 5-7 and 22-26. As such, Mylan would not directly infringe claims 5-7 or 22-26.

Mylan also would not infringe claims 5-7 or 22-26 of the '933 patent under the doctrine of equivalents. The doctrine of equivalents may not be used if it would result in the elimination of an element from the claim. *See Warner-Jenkinson*, 520 U.S. at 29. Here, any application of the doctrine of equivalents that could capture Natco's synthesis of sorafenib tosylate form I would result in the elimination of the claim elements reciting the use of sorafenib tosylate form II. Accordingly, the doctrine may not be applied to capture the recited methods, and Mylan would not infringe claims 5-7 or 22-26 of the '933 patent under the doctrine of equivalents.

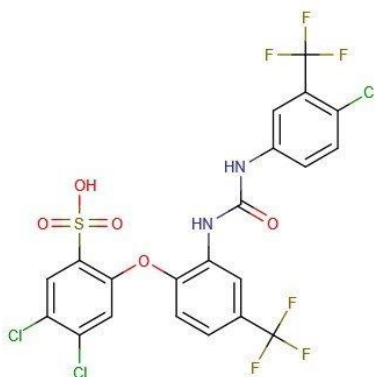
Claims 11-15 recite a pharmaceutical composition containing sorafenib tosylate form I and an additional "pharmaceutical agent." Mylan is seeking approval for a dosage form that includes only sorafenib tosylate as the API. Since Mylan is not seeking approval for compositions containing sorafenib tosylate and an additional pharmaceutical agent (or their use), Mylan will not infringe claims 11-15 of the '933 patent. *See Bayer*, 676 F.3d at 1321-22 (an ANDA that does not seek approval for a patented method of using a drug does not infringe and cannot induce infringement).

Mylan also would not infringe claims 11-15 under the doctrine of equivalents, because a finding that a composition containing sorafenib tosylate without any additional active ingredient is equivalent to a composition with an additional pharmaceutical agent would eliminate the additional "pharmaceutical agent" limitation of claims 11-15. *See Warner-Jenkinson*, 520 U.S. at 29.

VIII. Prior Art

A. PCT International Publication No. WO 97/04765 to Winkler et al. (“Winkler”)

Winkler was published on February 13, 1997, and having a priority date of July 25, 1995. Winkler is directed to the use of inhibitors of CoA-independent transacylase (CoA-IT) to treat cell proliferation and cancer. CoA-IT is an enzyme responsible for the movement of arachidonate between phospholipid molecular species of inflammatory cells. (Winkler, page 2) Winkler further discloses that 1-O-octadecyl-2-O-methyl-*sn*-glycero-3-phosphocholine (ET-18-O-CH₃) is a potent CoA-IT inhibitor which blocks the proliferation of cancer cells. Winkler also discloses that two other structurally different CoA-IT inhibitors can also block the proliferation of cancer cells in comparable fashion to ET-18-O-CH₃, only one of which is a ureido compound. (Winkler, page 7, ll. 4-10) Of the two ureido compounds disclosed in Winkler, the only active one is 2-[2-[3-(4-chloro-3-trifluoromethylphenyl) ureido]-4-trifluoromethyl phenoxy]-4,5-dichlorobenzene sulfonic acid (Compound I^a), a ureido compound which has the following structural formula:



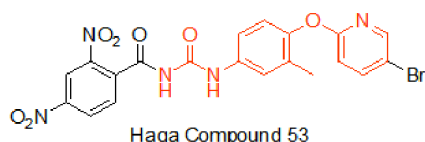
Winkler at 6, 11, Table 1, Compound I^a.

Compound I^a inhibits CoA-IT having and IC₅₀ of 6 μM against human leukemic cell line HL-60. *Id.* at 11, Table 1, Compound I^a. Compound II^b is also a ureido compound. However, it does not induce apoptosis of HL-60 cancerous cells. *Id.* at 11, Table 1, Compound II^b. Moreover, Compound I^a has the same ureido structure connected to a 4-chloro-3-trifluoromethylphenyl moiety at one end and two aromatic groups connected by oxygen at the other end of NH-CO-NH ureido moiety as found in sorafenib. Winkler further teaches pharmaceutically acceptable salts of the disclosed compounds. *Id.* at 3. A sodium salt of Compound I^a is described in Example 2. *Id.* at 9, 19.

B. U.S. Patent No. 4,863,924 to Haga et al. (“Haga”)

Haga was published on September 5, 1989 from U.S. Application Serial No. 06/939,025 filed on December 8, 1986. Haga discloses N-benzoyl urea compounds useful for the treatment of tumor or cancer and “which exhibit excellent antitumor activities ... without bringing about side effects.” Haga at col. 1, ll. 59-64. Haga teaches that his Compound 53 exhibits the highest increase life span (ILS) when administered intraperitoneally or orally to mice carrying p-388 leukemia cells. *Id.* at col. 22, Table 5, Compound 53 and col. 23, Table 6-3, Compound 53.

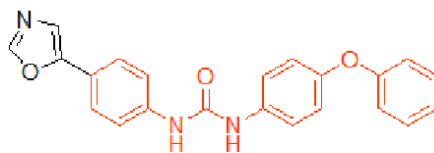
Compound 53 is preferred and has the following structure:



Haga’s Compound 53 is a structure similar to Winkler’s Compound I^a and the similarities are shown in red. *Id.* at col. 19, Table 4 and col. 3, ll. 8-9. Haga also teaches that his ureido compounds have poor solubility in both water and organic solvents. *Id.* at col. 26, ll. 3-4.

C. PCT International Publication No. WO 97/40028 to Armistead et al. (“Armistead”)

Published on October 30, 1997, and having an international filing date of April 21, 1997, Armistead claims priority to three U.S. applications, the earliest filed on April 23, 1996. Armistead teaches a class of compounds that are inosine monophosphate dehydrogenase inhibitors (IMPDH) which, in a preferred embodiment, may also be used to inhibit tumors and cancer in a mammal, for example lymphoma, leukemia and other forms of cancer. Armistead at 43, ll. 21-26). Among these compounds, Compound 21 is closest in structure to Winkler Compound I^a and the similarities are shown in red as illustrated below:



Armistead Compound 21

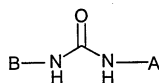
Compound 21 has a structure similar to Winkler’s compound I^a. *Id.* at 22, Table IB. Armistead also teaches that his compounds may be modified by appending appropriate functionalities to enhance biological properties including increased solubility. *Id.* at 32–33. Armistead further teaches pharmaceutically acceptable salts of the compounds of WO ‘028

including those derived from pharmaceutically acceptable inorganic and organic acids, also including tosylate. *Id.* at 29.

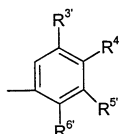
D. U.S. Patent Published Application 2008/0269265 to Miller et al. (“Miller ’265 publication”)

The Miller ’265 publication was published on October 30, 2008 from U.S. Application Serial No. 12/145,679 as a continuation of application Serial No. 09/776,936 filed on December 22, 1998. The Miller ’265 publication describes symmetrical and unsymmetrical substituted diphenyl ureas useful for the treatment of a cancerous cell growth mediated by raf kinase. In short, the Miller ’265 publication discloses anti-cancer compounds.

Miller’s aryl ureas include both aryl and heteroaryl analogues, which inhibit the raf pathway. Miller ’265 publication at [0004]. Both types of ureas have the same structural backbone. Miller’s ureas are illustrated as formula II:



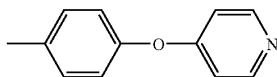
wherein, A can be a six member ring having the structure below



Miller ’265 publication at [0020], [0021].

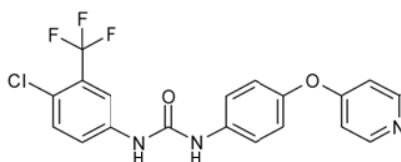
B can be substituted or unsubstituted, up to tricyclic aryl or heteroaryl moieties of up to 30 carbon atoms with at least one 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, where B is substituted it is substituted by one or more substituents selected from the group consisting of halogen, up to per-halo, and W_n , wherein n is 0-3 and W is independently selected from many other groups. *Id.* at [0022].

In the 5 tables of the Miller ’265 publication, Miller sets forth 144 substituted phenyl ureas, all of which are listed as displaying IC_{50} inhibitory concentration between 1 nM and 10 μ M for raf kinase. Miller ’265 publication at [0196]. Of Miller’s 144 compounds, only 22 are diaryl ether ureido compounds also containing a 4-chloro-3-trifluoromethyl phenyl group similar in structure to Winkler’s Compound I^a. Miller ’265 publication, Table 3. Of this group of 22 compounds, only compound 102 contains R2:



R2 as used in compound 102 is the most frequently deployed sidechain in the compounds disclosed in the Miller '265 publication and is a tested moiety in every compound permutation considered in Tables 1 and 2. In particular, in Table 1, compounds 9, 12, 17 and 25 contain this moiety; in Table 2, compounds 38, 81, 82 and 83 contain this moiety; in Table 3, compounds 102, 118, and 119 contain this moiety; and in Table 4, compounds 127, 132-141, and 144 contain this moiety.

In Table 3, the Miller '265 publication discloses Compound 102, a 2-substituted-5-(trifluoromethyl)phenyl urea having the structure below:



In methods A16 and A20, the Miller '265 publication discloses carbamoyl substituted compounds useful for synthesis of substituted anilines (method A16) and 2-(N-methylcarbamoyl)pyridines (method A20). *Id.* at [0151], [0152], [0161], [0162]. The Miller '265 publication also discloses 2-(N-methylcarbamoyl) chloropyridine. Miller '265 publication at [0162]. The Miller '265 publication also discloses a combinatorial method for synthesis of diphenyl ureas using triphosgene. Miller '265 publication at [0185].

In addition to the compounds set forth in Miller's tables, the Miller '265 publication also teaches pharmaceutically acceptable salts including basic salts of inorganic and organic acids and acid salts of inorganic bases as follows:

The present invention is also directed to pharmaceutically acceptable salts of Formula I. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, sulphonic acid, acetic acid, trifluoroacetic acid, malic acid tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2} , Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Miller '265 publication at [0044].

Miller's pharmaceutical compositions also include a compound of Formula I, and a physiologically acceptable carrier. Miller '265 publication at [0055]. Miller further discloses tablets containing the active ingredient as follows:

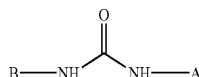
Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable **excipients** which are suitable for the manufacture of tablets. These excipients may be, for example, inert **diluents**, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; **granulating and disintegrating agents**, for example, corn starch, or alginic acid; and **binding agents**, for example magnesium stearate, stearic acid or talc.

Miller '265 publication at [0057], emphasis added.

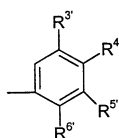
E. U.S. Patent No. 7,517,880 to Miller et al. ("Miller '880 patent")

The '880 patent issued on April 14, 2009 from U.S. Application Serial No. 10/060,396 ("the '396 application") filed on February 1, 2002 as a continuation of application Serial No. 09/458,015, filed December 10, 1999, now abandoned, which is a continuation of application Serial No. 09/285,522, filed December 22, 1998, now abandoned, which claims benefit of Provisional Application No. 60/126,439, filed December 22, 1997, now abandoned.

Like the Miller '265 publication, the Miller '880 patent teaches biaryl asymmetric ureas which inhibit p38 mediated events including advanced cancer and cancer. (Miller '880 patent, Col. 4, ll. 29-336; ll. 62-65) The ureas disclosed in the Miller '880 patent are illustrated as formula I:

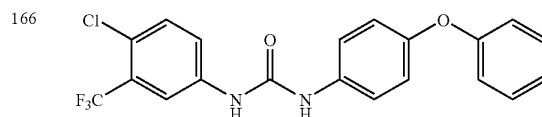


wherein, A can be a six member ring having the structure below



B can be substituted or unsubstituted, up to tricyclic aryl or heteroaryl moieties of up to 30 carbon atoms with at least one 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, where B is substituted it is substituted by one or more substituents selected from the group consisting of halogen, up to per-halo, and W_n , wherein n is 0-3 and W is independently selected from many other groups. Miller '880 patent at col. 5, ll. 25-62. These ureas can be used to inhibit p38 kinase and also raf kinase, both implicated in cancer treatment. *Id.* at col. 18, ll. 11-12. In short, the Miller '880 patent discloses anti-cancer compounds.

In the 5 tables of the Miller '880 patent all compounds are listed as displaying IC_{50} inhibitory concentration between 1 nM and 10 μM for p38 kinase. Miller '880 patent at col. 97, ll. 102. In Table 5 of the Miller '880 patent, among many miscellaneous ureas, there is Compound 166 which has the formula below:



Compound 166 has a structure that is closest to Winkler's Compound I^a.

Like the Miller '265 publication, the Miller '880 patent discloses carbamoyl substituted compounds useful for synthesis of substituted anilines (method A16) and 2-(N-methylcarbamoyl)pyridines (method A20). Miller '880 patent at col. 42, ll. 1-34; Col. 44, ll. 15-51. Miller '880 also discloses 2-(N-methylcarbamoyl)chloropyridine. The Miller '880 patent

further teaches pharmaceutically acceptable salts including basic salts of inorganic and organic acids and acid salts of inorganic bases. Miller '880 patent at col. 11-12.

Therefore, the Miller '880 patent teaches a structure similar to sorafenib, wherein Compound 166 of the Miller '880 patent selected based on Winkler's Compound I^a structure has a phenyl group in lieu of a pyridine moiety bearing a methylcarboxamide.

Moreover, the Miller '880 patent also teaches pharmaceutically acceptable salts including basic salts of inorganic and organic acids and acid salts of inorganic bases. Miller '880 patent, Col. 11, l. 65 – Col. 12, l. 20.

Miller's pharmaceutical compositions also include a compound of Formula I, and a physiologically acceptable carrier. Miller '880 patent, Col. 15, ll.11-13. Miller further discloses tablets containing the active ingredient as follows:

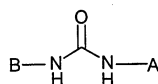
Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable **excipients** which are suitable for the manufacture of tablets. These excipients may be, for example, inert **diluents**, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; **granulating and disintegrating agents**, for example, corn starch, or alginic acid; and **binding agents**, for example magnesium stearate, stearic acid or talc.

Miller '880 patent, Col. 15, ll. 31-39, emphasis added.

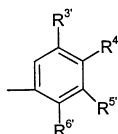
F. PCT International Publication No. WO 99/32436 to Miller et al. (Miller PCT)

Published on July 1, 1999, and having an international filing date of December 22, 1998, Miller PCT claims priority to U.S. Application Serial No. 08/996,344 filed on December 22, 1997. Miller has 5 inventors in common with the '576 patent including Riedl, a named co-inventor.

In Compound 102, Miller PCT describes a raf kinase inhibitor that has the same structure as sorafenib, except that Miller PCT's raf kinase inhibitor does not contain a N-methyl carbamoyl moiety on the pyridine ring at a meta position to the oxygen ring of the bridge -L-O-L¹ structure. More particularly, Miller PCT describes symmetrical and asymmetrical substituted diphenyl ureas useful for the treatment of cancerous cell growth mediated by raf kinase. In short, Miller PCT discloses anti-cancer compounds. Miller PCT at 2. Miller PCT's compounds are inhibitors of the raf kinase pathway. Miller discloses the p21^{ras} oncogene, a major contributor to the development and progression of human solid cancers, and that inhibiting raf kinase results in inhibiting active ras and thus, the inhibition of the growth of a variety of tumors. *Id.* Miller PCT's aryl ureas include both aryl and heteroaryl analogues, which inhibit the raf pathway. *Id.* Both types of ureas have the same structural backbone. Miller PCT's ureas are illustrated on page 5 as formula II:



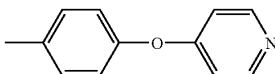
wherein, A can be a six member ring having the structure below



Miller PCT at 5, l. 4.

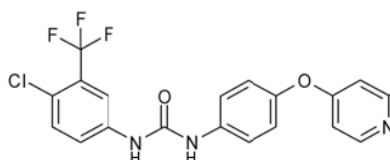
B can be substituted or unsubstituted, up to tricyclic aryl or heteroaryl moieties of up to 30 carbon atoms with at least one 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, where B is substituted it is substituted by one or more substituents selected from the group consisting of halogen, up to per-halo, and W_n , wherein n is 0-3 and W is independently selected from many other groups. Miller PCT at 5.

In his 5 tables, Miller PCT sets forth 144 substituted phenyl ureas, all of which are listed as displaying IC_{50} inhibitory concentration between 1 nM and 10 μ M for raf kinase. (Miller PCT at 74, l. 20) Of Miller PCT's 144 compounds only 22 are diaryl ether ureido compounds also containing a 4-chloro-3-trifluoromethyl phenyl group similar in structure to Winkler's Compound I^a. (Miller, Table 3) Of this group of 22 compounds, only compound 102 contains R2, which is:



R2 as used in compound 102 is the most frequently deployed sidechain in the Miller PCT compounds and is a tested moiety in every compound permutation considered in Tables 1 and 2. In particular, in Table 1, compounds 9, 12, 17 and 25 contain this moiety; in Table 2, compounds 38, 81, 82 and 83 contain the R2 moiety; in Table 3, compounds 102, 118, and 119 contain this moiety; and in Table 4, compounds 127, 132-141, and 144 contain this moiety.

In Table 3, Miller PCT discloses Compound 102, a 2-substituted-5-(trifluoromethyl)phenyl urea having the structure below:



Miller PCT's Compound 102 is almost the entire sorafenib structure except that the methyl carbamoyl or carboxamide substituent at the meta position to the oxygen of the bridge structure is missing.

In methods A16 and A20 at pages 46 and 49, respectively, Miller PCT discloses carbamoyl substituted compounds useful for synthesis of substituted anilines (method A16) and 2-(N-methylcarbamoyl)pyridines (method A20). 2-(N-methylcarbamoyl)chloropyridine disclosed by Miller PCT on page 49 is the same compound as 4-chloro-2-pyridinecarboxamide used in the '576 patent in the synthesis of sorafenib or compound 42 disclosed at Col. 46, ll. 15-20 of the '576 patent. Miller PCT also discloses a combinatorial method for synthesis of diphenyl ureas using triphosgene. Miller PCT at 59.

In addition to the compounds set forth in Miller PCT's tables, Miller PCT also teaches pharmaceutically acceptable salts including basic salts of inorganic and organic acids and acids salts of inorganic bases as follows:

The present invention is also directed to pharmaceutically acceptable salts of Formula

I. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, sulphonic acid, acetic acid, trifluoroacetic acid, malic acid tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2} , Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Miller PCT, page 9, ll. 9-23

Miller PCT also teaches that the alleged invention also includes pharmaceutical compositions including a compound of Formula I, and a physiologically acceptable carrier. Miller PCT at 13. Therefore, Miller PCT teaches a structure similar to sorafenib, except that Miller PCT's Compound 102 does not have the methylcarboxamide substituent on the pyridine ring.

G. PCT International Publication No. WO 99/32106 to Dumas et al. (Dumas)

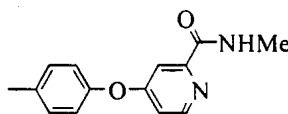
Published on July 1, 1999, and having an international filing date of December 22, 1998, Dumas claims priority to U.S. Application Serial No. 08/996,343 filed on December 22, 1997.

As in Miller PCT, Dumas' compounds are asymmetrical substituted diaryl ureas that are useful to treat cancers by inhibiting raf kinase. In particular, as described in Miller PCT's aryl ureas, Dumas' aryl ureas include both aryl and heteroaryl analogues, which inhibit the raf pathway (Dumas at 2) and are useful in treating solid cancers such as, for example, carcinomas (e.g., lungs, pancreas, thyroid, bladder or colon, myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma). Dumas at 2, ll. 12-14. Dumas' ureas are illustrated on page 2 as formula I:



wherein B is generally an unsubstituted or substituted, up to tricyclic, aryl or heteroaryl moiety with up to 30 carbon atoms with at least one 5 or 6 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur. A is a heteroaryl moiety discussed in more detail below. Dumas at 2.

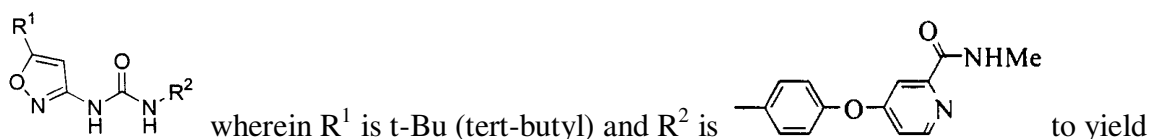
In Compound 101, R2 is shown below:



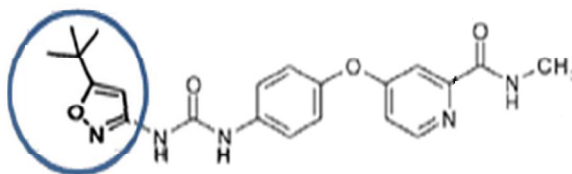
The R2 moiety is a frequently tested moiety in almost every compound permutation considered in Dumas' many tables. In particular, in Table 2, compounds 182, 215, 218 and 261 contain this R2 moiety. In Table 4, compound 352 also contains this R2 moiety. In Table 5, compound 393 also contains the R2 moiety.

Compound 101 would be considered by a person of ordinary skill in the art as a preferred compound. In Compound 101, R² does not have any other substituents on its rings other than methyl carbamoyl which enhances its solubility, and therefore it would be the best candidate for further consideration among the seven potential candidates listed in Table 1. Further, Dumas included Compound 101 among specific examples of preferred 5,3-isoxazolyl ureas as compound N-(5-tert-butyl-3-isoxazolyl)-N'-(4-(4-(2 carbamoyl) pyridyl) oxyphenyl) urea having the formula shown above. (Dumas, page 13, ll. 32-33)

Compound 101, a 5-substituted-3-isoxazolyl urea has the structure below:



Compound 101, which has a methyl carbamoyl moiety on a pyridine ring in an ortho position to the pyridine nitrogen or a meta position to the oxygen on the bridge structure to provide the following structure:



Dumas at 87, Table 1.

Dumas' structure is similar to sorafenib except instead of a 2-chloro-5-(trifluoromethyl)phenyl substituent at the B position of the A-D-B backbone of the '576 patent, Dumas has a 5-tertbutyl-3-isoxazolyl group as shown above in the circle. Like Miller PCT, all of Dumas' compounds are listed as displaying IC₅₀ inhibitory concentration for raf kinase of between 1 nM and 10 μM. Dumas at 112, l. 4.

In methods B6 and B10 at pages 52 and 55, respectively, Dumas discloses carbamoyl substituted compounds useful for synthesis of substituted anilines (method B6) and 2-(N-methylcarbamoyl)pyridines (method B10). Dumas further discloses 2-(N-methylcarbamoyl)chloropyridine. Dumas at 55. In method C8, Dumas also discloses combinatorial methods for the synthesis of diphenyl ureas using triphosgene via the same method disclosed in Miller (Dumas, page 70). Therefore, the synthesis method of sorafenib is disclosed in Dumas as well.

Like Miller, in addition to the compounds set forth in Dumas' tables, Dumas also teaches pharmaceutically acceptable salts including basic salts of inorganic and organic acids and acids

salts of inorganic bases (Dumas, page 18, ll. 1-16). Further, like Miller, Dumas teaches that the alleged invention also includes pharmaceutical compositions that include compounds described above and a physiologically acceptable carrier. Dumas at 17.

H. Khire, U. R. et al., Omega-carboxypyridyl substituted ureas as raf kinase inhibitors: SAR of the amide substituent, Bioorganic & Medicinal Chemistry Letters 14, 783-786, (2004)(“Khire”).

Published in 2004, this scientific article authored by Khire *et al.* includes among the other authors J. Dumas, J. Wood, T. B. Lowinger, M. Monahan, R. Natero, J. Renick, B. Riedl, R. Sibley and R. A. Smith, who together with Khire are among the co-inventors of the '834 patent. In this article, the authors describe how a lead compound was identified by screening a combinatorial chemistry library that exhibited an IC₅₀ value of 1100 nM against recombinant human raf-1 kinase. In short, the authors/inventors of the '834 patent describe how their use of combinatorial chemistry for the “optimization” of the lead compound led to a series of potent, orally active raf-1 kinase inhibitors and that this culminated in the identification of a clinical candidate BAY 43-9006, another name for sorafenib. Khire at 783.

I. Wilhelm S. et al., Discovery and development of sorafenib: a multikinase inhibitor for treating cancer, Nature Reviews Drug Discovery 5, 835–844, (2006)(“Wilhelm”).

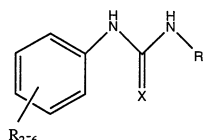
Published in 2007, this scientific article authored by S. Wilhelm, includes among the other authors T. Lowinger, J. Dumas, R. A. Smith, also co-inventors of the '834 patent. This article provides, *inter alia*, a historical setting for the development of sorafenib. In the Abstract, the authors state that the introduction and refinement of rapid, high-throughput screening (HTS) technologies over the past decade, had greatly facilitated this targeted discovery and development process. Specifically, around 1989, high-throughput *in vitro* screening (HTS) and combinatorial chemistry² rapidly grew as a major paradigm for discovery of new chemicals. Wilhelm at 836. The authors recognized that in 1994, when the project team was formed, “the reagents and assays were available to identify a raf kinase inhibitor. A scintillation proximity assay for the HTS and identification of selective Raf/MEK/ERK enzyme inhibitors had already been developed by McDonald *et al.* at Glaxo-Wellcome Inc.,” showing that this approach was feasible and did not require undue experimentation. Tumor cell lines that contained oncogenic k-ras and/or b-raf mutations demonstrated upregulated signaling through the Raf/MEK/ERK pathway. Such tumor lines would be vital for performing the necessary in vitro and human tumor xenograft studies required to identify and select candidate raf kinase inhibitors for further evaluation in Phase I clinical trials. Wilhelm states that “the essential tools were available to

² Combinatorial chemistry encompasses various technologies for the rapid synthesis of large collections of compounds to facilitate the identification of new active compounds for drug targets by HTS techniques. Wilhelm at 836.

proceed with the discovery and development of a novel targeted raf1 kinase inhibitor for the treatment of cancer.” *Id.* at 836.

J. PCT International Patent Publication No. WO 96/40673 to Tang, P. et al. (“Tang”)

Published on December 19, 1996 and having an international filing date of June 4, 1996, Tang discloses that ureido compounds have broad tyrosine kinase inhibition activity used to inhibit cancer. Specifically, Tang discloses molecules capable of modulating tyrosine signal transduction to prevent and treat cell proliferative disorders or cell differentiation disorders associated with particular tyrosine kinases by inhibiting one or more abnormal tyrosine kinase activities. These molecules are ureido compounds of the formula:



wherein X is O or S, R₁ is selected from the group consisting of optionally substituted aryl, alkylaryl, and heteroaryl; and R₂₋₆ are independently selected from the group consisting of hydroxy, H, alkyl, alkoxy, CN, nitro, halo, trihalomethyl, amide, carboxamide, sulfonyl, and sulfoxamide. Tang at 3. Sorafenib is a ureido compound having tyrosine kinase inhibitory activity, similar to that of Tang’s ureido compounds.

K. Lipinski, C. A. et al., Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings, Advanced Drug Delivery Reviews 23, 3-25, (1997) (“Lipinski”).

Published in 1997, Lipinski conducted experimental and computational studies of the World Drug Index database to estimate solubility and permeability in the discovery and development phase of drug-like lead compounds. Lipinski found that at the discovery stage “the rule of 5” can be used to predict poor absorption or permeation of lead compounds. Lipinski’s “rule of five” predicts that poor adsorption or permeation of a drug-like compound is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, the molecular weight is greater than 500 and the calculated log P(ClogP) is greater than 5. (Lipinski at Abstract.) Further, in describing the selection a lead compound, Lipinski stated:

The physico-chemical profile of current leads i.e. the 'hits' in HTS screens now no longer depends on compound solubility sufficient for in vivo activity but depends on: (1) the medicinal chemistry principles relating structure to in vitro activity; (2) the nature of the HTS screen; (3) the physico-chemical profile of the compound set being screened and (4) to human decision making, both overt and hidden as to the acceptability of compounds as starting points for medicinal chemistry structure activity relationship (SAR) studies.

One of the most reliable methods in medicinal chemistry to improve in vitro activity is to incorporate properly positioned lipophilic groups. For example, addition of a single methyl group that can occupy a receptor 'pocket' improves binding by about 0.7 kcal/mol [6]. By way of contrast, it is

Lipinski at 5.

Through his studies, Lipinski concluded that:

Combinatorial chemistry and high throughput screening (HTS) techniques are used in drug research because they produce leads with an efficiency that compares favorably with 'rational' drug design and, perhaps more importantly, because these techniques expand the breadth of therapeutic opportunities and hence the leads for drug discovery. Established methodology allows the medicinal chemist, often in a relatively short time, to convert these novel leads to compounds with in vitro potency suitable to a potential drug candidate. This stage of the discovery process is **highly predictable**.

...

Computational methods in the early discovery setting need to deal with large numbers of compounds and serve as filters which direct chemistry SAR towards compounds with greater probability of oral activity.

...

Drug discovery requires a starting point - a lead. Hence the current literature correctly focuses on improving *in vitro* activity detection by optimizing chemical diversity so as to maximize coverage of three-dimensional receptor space. Assuming this goal is not compromised by physico-chemical calculations, we believe a competitive advantage accrues to the organization that can identify compound sets likely to give leads more easily converted to orally active drugs.

Lipinski at 23, emphasis added.

L. Curatolo, W., Physical chemical properties of oral drug candidates in the discovery and exploratory development settings, PSTT Vol. 1, No. 9, 387-393, December 1998 (“Curatolo”).

Published in in December 1998, Curatolo advanced the studies conducted by Lipinski. Curatolo discusses physical chemical properties of oral drug candidates in the discovery and exploratory settings at the time that the compounds of the '834, '576, and '623 patents were developed. These properties include solubility and permeability. Curatolo notes the advent of high through-put *in vitro* screening as a major technique for discovery of new chemical leads, which occurred around 1989. He remarks that “[t]his approach was highly successful in the discovery of novel structures with superb *in vitro* potency, but ignored issues of drug absorption and metabolism” so that the lead compounds were no longer drug-like. Curatolo at 388.

Curatolo explains that oral efficacy is a function of potency and oral bioavailability. Oral bioavailability is a function of the fraction of drug absorbed by the intestine into the portal blood, and of the percentage first-pass hepatic extraction. The fraction of drug absorbed into the portal blood is a function of the solubility of the drug relative to dose, and the intrinsic permeability of the intestinal wall to the drug, reflected in a permeability measurement or an absorption rate constant. Curatolo at 388. Selecting a lead compound which is likely to have physico-chemical properties consistent with good absorption should be balanced with selecting an efficacious but non-absorbed compound. Curatolo teaches that target binding activity of a lead compound should be balanced with a desire for increased permeability. Accordingly, once efficacious lead compounds are identified, applying filters to obtain a compound of increased permeability and solubility would enhance the chances of a lead compound for survival through preclinical studies.

M. U.S. Patent App. Pub. No. 2003/0232765 to Carter et al. (“Carter”)

Carter published on December 18, 2003 and discloses a generic chemical structure of aryl ureas (formula I) that encompasses sorafenib. Carter at ¶¶ 12-33. The tosylate salt of sorafenib is disclosed specifically at paragraph 52 of Carter. Further, the examples and experiments disclosed in Carter use sorafenib tosylate. *Id.* at ¶ 91. Carter also discusses the use of excipients in the formulation of aryl urea compounds as an oral dosage form. *Id.* at ¶ 65. The aryl urea

compound may be combined with another chemotherapeutic agent that is a cytotoxic or cytostatic agent. *Id.* at ¶¶ 38, 48. Carter also states that formulations of aryl urea compounds (e.g., sorafenib tosylate) may be used to treat diverse cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. *Id.* at ¶¶ 36, 45.

N. PCT application no. WO00/042012 to Riedl et al. (“the ’012 publication”)

The ’012 publication published on July 20, 2000 and discloses the synthesis of sorafenib tosylate. The ’012 publication also discloses the tosylate salt of sorafenib. ’012 publication at 6.

O. J. Keith Guillory, “Generation of Polymorphs, Hydrates, Solvates, and Amorphous Solids” 183 in Polymorphism in Pharmaceutical Solids (H.G. Brittain ed.) (1999) (“Guillory”)

Guillory provides a description of the state of the art of polymorph isolation as of 1999. Guillory focuses his discussion on organic pharmaceutical agents and emphasizes the importance of isolating and analyzing polymorphic crystalline forms of those compounds. Guillory at 184. “It is incumbent on the manufacturer of a new drug substance to show that due diligence has been employed to isolate and characterize the various solid-state forms of a new chemical entity.” *Id.* at 185. Guillory also states that “[i]t is essential to ascertain whether the crystalline material that results from a synthetic procedure is thermodynamically stable before conducting pivotal trials, since a more stable form may be obtained subsequently, and it may be impossible to produce the metastable form in future syntheses.” *Id.* at 184. Thus, Guillory provides a clear motivation to one of ordinary skill in the art to identify and characterize polymorphs of a pharmaceutically active chemical compound, in particular the thermodynamically stable form.

Guillory provides extensive details on how one of skill in the art might isolate polymorphs of a chemical compound and also how to isolate the thermodynamically stable form. Guillory offers numerous strategies as a “‘screening’ protocol” for isolation of polymorphs. *Id.* at 186. The described techniques include sublimation, crystallization from a single solvent, evaporation from a binary mixture of solvents, vapor diffusion, thermal treatment, crystallization from the melt, pH adjustment, thermal desolvation, crystal growth in the presence of additives, and grinding. *Id.* at 185-202. In discussing crystallization from a single solvent, Guillory initially proposes forming saturated solutions of the compound to be crystallized that may be left undisturbed for a “reasonable period of time.” *Id.* at 188. If such passive efforts are unsuccessful, alternatives of scratching the interior of the vessel or seeding with nuclei of the same material may be pursued. *Id.*

A “commonly used crystallization method” may also be employed where the temperature of the solution may be manipulated to promote crystallization. *Id.* at 189. As a general rule, Guillory offers that “it may be assumed that unstable crystals form preferentially at lower temperatures, while at higher temperatures stable forms are to be expected.” *Id.* at



CONFIDENTIAL
November 9, 2015
Page 73

187. Regarding isolation of the thermodynamically stable polymorph, Guillory states that “[t]he relative solubility of two polymorphs is a convenient measure of their relative free energies. The polymorph having the lower solubility is the more thermodynamically stable form, i.e., the form with the lower free energy at the temperature of the solubility measurement.” *Id.* at 190-91. Guillory also offers the theory that “at equilibrium the product of any crystallization experiment must be the stable form, regardless of the solvent system.” *Id.* at 191. Guillory also discloses the additional method, where thermal treatment of samples of the material may be employed to obtain polymorphic forms of the compound. *Id.* at 195-97. Guillory notes that in some instances, “it is often possible to prepare the higher melting polymorph by thermal treatment.” *Id.*

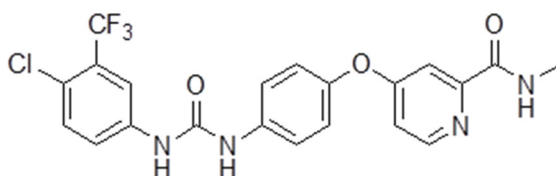
In sum, Guillory provides one having ordinary skill in the art with a clear motivation to obtain polymorphs of a pharmaceutically active compound. In particular, Guillory specifically states that it is important to isolate the thermodynamically stable polymorph. Finally, Guillory provides numerous methods that may be used to screen for polymorphic forms.

IX. Obviousness

A. U.S. Patent No. 7.351,834

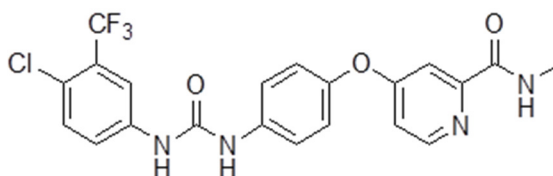
i. Claim 1 is Obvious in View of Winkler, Haga and Solubility Optimization

Claim 1 is a generic claim, reciting, among others the compound sorafenib, having the structure set forth below:



When analyzing the validity or invalidity of a generic claim, it is well settled law that “[a] single, obvious species within a claimed genus renders the claimed genus unpatentable under § 103.” *Ex parte Kubin*, 83 U.S.P.Q.2d 1410 (B.P.A.I. 2007), a precedential decision affirmed by the Federal Circuit in *In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009). Accordingly, if the sorafenib specie is obvious in view of the prior art, claims 1, 2, 4, 5, 24, 25, 28, 29, 31 and 35-39, which recite sorafenib generically and/or as a specie would also be invalid for obviousness as well.

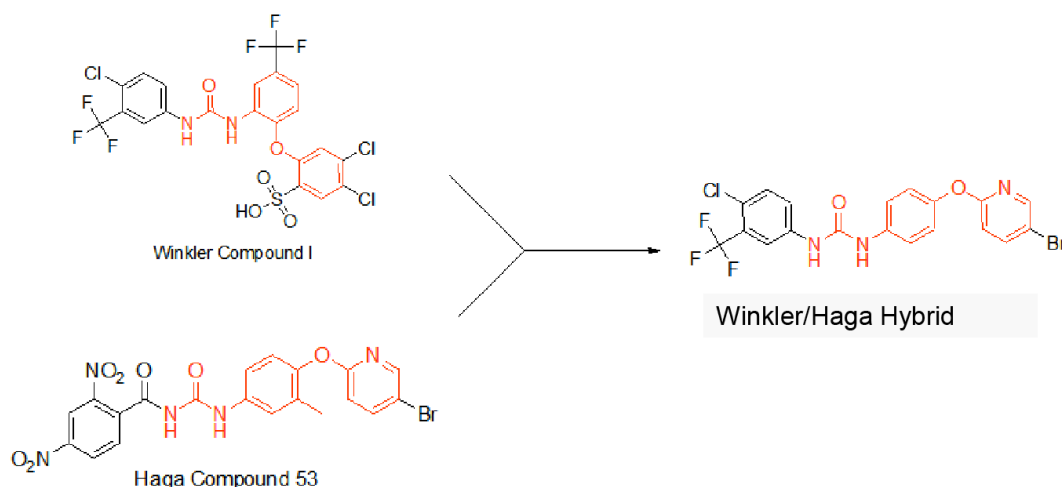
1. Selection of lead compound



As explained above, it was known in the prior art from Winkler that an asymmetrical substituted ureido compound having a 4-chloro-3-trifluoromethylphenyl group and other diaryl ether groups, such as Compound I^a, can inhibit CoA-IT by blocking cancer cells proliferation³. Of the two ureido compounds disclosed in Winkler, Compound I^a is the only one exhibiting cancer cells antiproliferative activity, while the other ureido compound II^b was found to be inactive and not capable of inducing cell apoptosis. Winkler at 11, Table 1. Accordingly, one of ordinary skill in the art seeking to provide a lead compound with good antiproliferative activity would select for further investigation the only ureido compound that can induce cell apoptosis disclosed in Winkler, namely Compound I^a.

³ It was also known from Tang that ureido compounds have broad tyrosine kinase inhibition activity. Tang at 3.

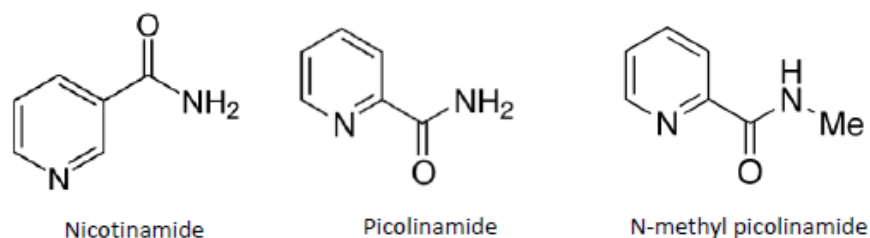
Among its preferred compounds, Haga discloses Compound 53 as the closest structure to Winkler's Compound I^a. Like Winkler, Haga's Compound 53 has antiproliferative properties but like other Haga compounds, it has poor solubility. One of ordinary skill in the art would then consider Haga's ureido Compound 53 that has a similar structure to Winkler's Compound I^a to test the resulting hybrid for anti-cancer activity. To design a ureido compound with anti-cancer activity, one of ordinary skill in the art would find it obvious to make sorafenib by taking Winkler's Compound I^a and modify it in view of Haga's Compound 53, which has superior anti-cancer activity as evidenced by its high increase life span (ILS) against cancerous cells. The skilled artisan would have a reasonable expectation of success because Compound I^a could induce apoptosis of cancerous cells at 6μM. *Id.* at 11, Table 1. Further, Haga's Compound 53 would be recommended by its high increase life span (ILS) value against leukemia cells. One of ordinary skill in the art would combine the Winkler and Haga compounds to obtain a Winkler-Haga hybrid as illustrated below:



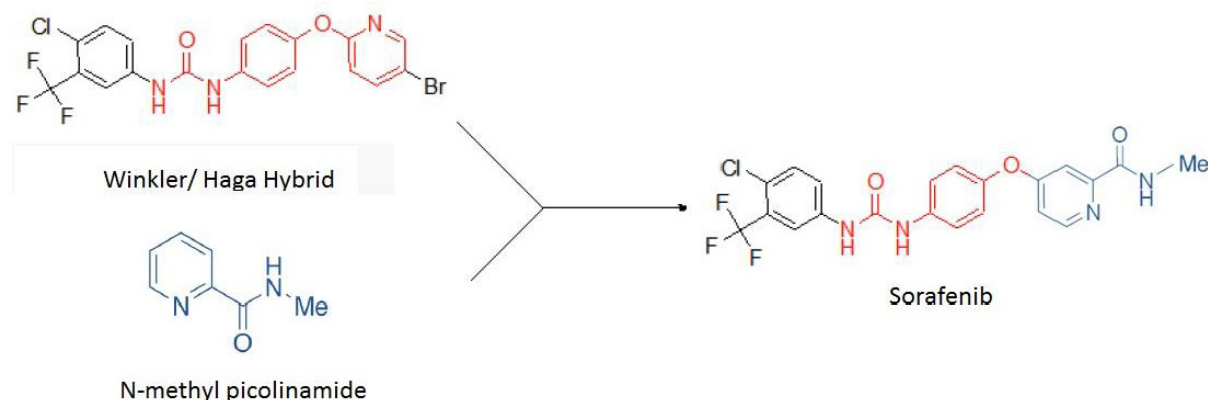
However, Haga also teaches that his compounds disclosed are poorly soluble and their solubility should be optimized. Haga at col. 26, ll. 3-6. Therefore, one of ordinary skill in the art would try to improve its solubility in order to improve the compound's ability to bind to an enzyme receptor.

2. Enhanced Solubility and Improved Binding in the Enzyme Receptor Binding as the Reason for Modifying the Winkler-Haga Hybrid

It was also known since at least 1996, that nicotinamide and picolinamide have high solubility in water, 5×10^5 mg/L and 1.8×10^5 mg/L, respectively (data from SRC PhysProp Database).



SRC PhysProp Database further teaches N-methyl picolinamide, as an obvious derivative of picolinamide, which one of skill in the art seeking to enhance the solubility of an anti-cancer drug while maintaining its potency and improving binding in an enzyme receptor pocket, as disclosed by Lipinski above, would find it obvious to incorporate the N-methylpicolinamide structure into the Winkler-Haga hybrid, inevitably arriving to the sorafenib structure. Accordingly, incorporating N-methylpicolinamide, shown in blue, into the Winkler-Haga hybrid would enhance its solubility resulting in better bioavailability and also enhanced binding to an enzyme receptor pocket. The resulting sorafenib structure is illustrated below:



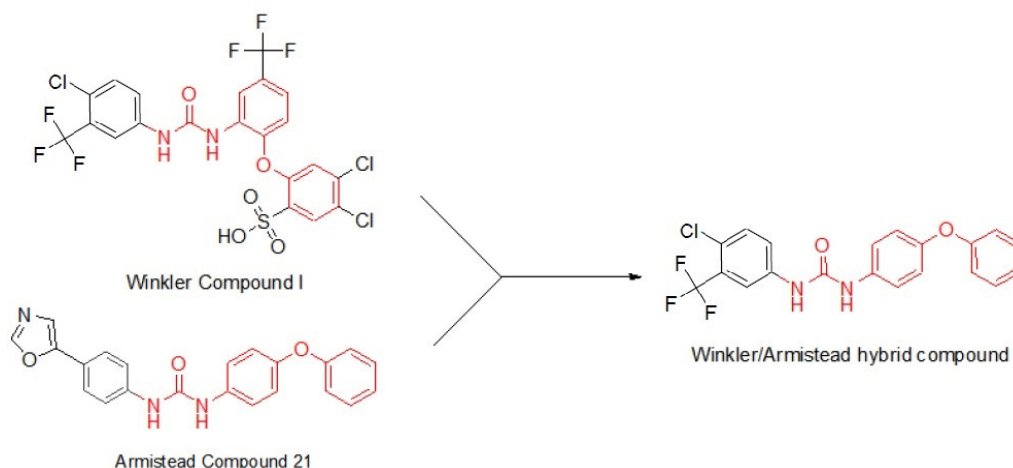
Accordingly, claim 1 is invalid under 35 U.S.C. § 103(a) as obvious over the prior art of Winkler in view of Haga and the enhanced solubility provided by N-methyl picolinamide.

ii. Claim 1 is Obvious in View of Winkler, Armistead and Solubility Optimization

1. Selection of Lead Compound

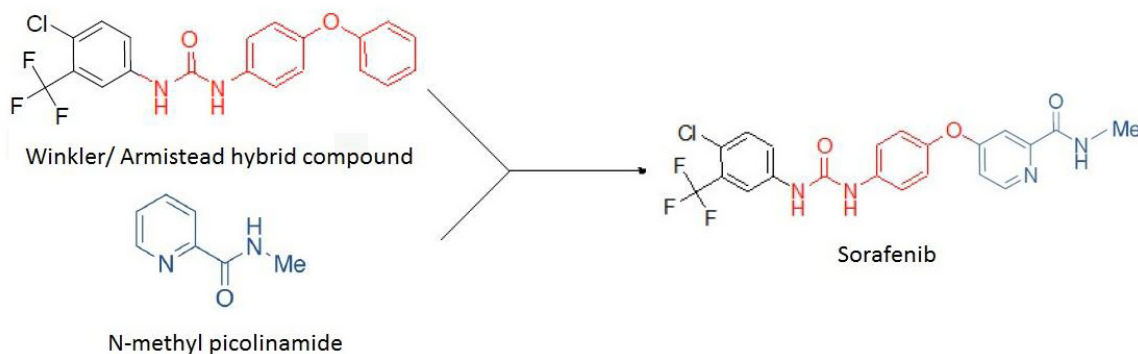
The selection of Winkler's ureido Compound I^a was discussed above. Starting with Winkler's Compound Ia, one of ordinary skill in the art would consider Armistead Compound 21 because it has the closest structure to Compound I^a and can be used to inhibit cancerous tumors. To design a ureido compound with anti-cancer activity, one of ordinary skill in the art would find

it obvious to make sorafenib by taking Winkler's Compound I^a and modify it in view of Armistead Compound 21 to obtain a Winkler-Armistead hybrid. A Winkler-Armistead hybrid is illustrated below:



2. Enhanced Solubility and Improved Binding in the Enzyme Receptor Binding as the Reason for Modifying the Winkler/Armistead Hybrid Compound

Further, Armistead also teaches that his compounds may be modified to increase their solubility. Therefore, one of ordinary skill in the art would try to improve the solubility of the Winkler-Armistead hybrid in order to improve the compound's ability to bind to an enzyme receptor and thus inhibit the growth of cancer cells. The enhanced solubility provided by replacing one of the phenyl groups with N-methylpicolinamide would inevitably result in the sorafenib structure, as discussed above. Accordingly, incorporating N-methylpicolinamide into the Winkler-Armistead hybrid would enhance its solubility resulting in better bioavailability and enhanced binding to an enzyme receptor pocket. The resulting sorafenib structure is illustrated below:

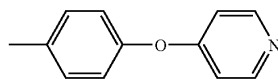


Accordingly, claim 1 is invalid under 35 U.S.C. § 103(a) as obvious over the prior art of Winkler in view of Armistead and the enhanced solubility provided by N-methyl picolinamide.

iii. **Claim 1 is Obvious in View of Winkler, the Miller '265 Publication and Solubility Optimization**

1. **Selection of Lead Compound**

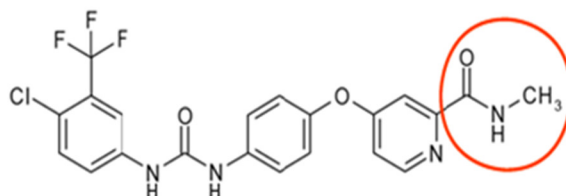
The selection of Winkler's ureido Compound I^a was discussed above. The further selection of Compound 102 in Table 3 of the Miller '265 publication based on the structure of Winkler's Compound I^a was also discussed above in connection with the Miller '265 publication. Specifically, the Miller '265 publication lists 22 structures similar to Winkler's Compound I^a.



However, based on R2 of , tested in every compound permutation of Tables 1 and 2 of Miller '265, Compound 102 emerges as the natural lead compound.

Miller's Compound 102 has the same backbone structure as sorafenib that is claimed in claim 1 of the '834 patent. For example, the backbone of the '834 patent is A-D-B, wherein D is -NH-C(O)-NH-, A is a substituted moiety of up to 40 carbon atoms, and B is a substituted or unsubstituted, up to tricycle aryl or heteroaryl moiety of up to 30 carbon atoms. '834 patent at col. 2, ll. 15-17, ll. 26-28. 'Moreover, 2-(N-methylcarbamoyl) chloropyridine disclosed by Miller at para. [0162] is the same compound as 4-chloro-2-pyridinecarboxamide used in the '834 patent in the synthesis of sorafenib or compound 42 disclosed at col. 49, ll. 24-28 of the '834 patent. The Miller '265 publication also discloses a combinatorial method for synthesis of diphenyl ureas using triphosgene which is similar to a method utilized in the '834 patent for the same purpose. Miller '265 publication at [0185]; '834 patent at col. 39, ll. 20 et seq.

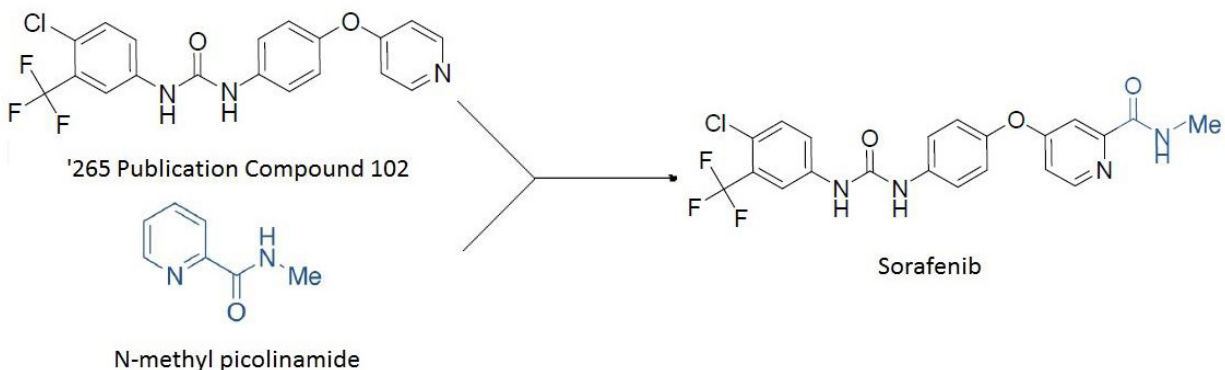
By comparison to sorafenib, Miller's Compound 102 is missing an N-methylcarbamoyl moiety as shown below:



Miller' Compound 102 has more than a mere structural similarity to sorafenib, it is recognized as a potent raf kinase inhibitor having an IC_{50} of between 1 nM and 10 μ M used for the treatment of a cancerous cell growth mediated by raf kinase. Miller '265 publication at [0020] and [0196]. When the claimed invention and structurally similar prior art species share any useful property, that will generally be sufficient to motivate an artisan of ordinary skill to make the claimed species. *In re Dillon*, 919 F.2d 688, 711 (Fed. Cir. 1990) (*en banc*), which was not overruled by the Otsuka decision. Accordingly, Winkler in view of the Miller '265 publication in combination with picolinamide/N-methyl picolinamide would render obvious sorafenib and thus invalidate all claims that recite it generically or as specie.

2. **Enhanced Solubility and Improved Binding in the Enzyme Receptor Binding as the Reason for Modifying Compound 102 as Disclosed in the Miller '265 Publication**

It was also known since at least September 5, 1989 that diphenyl ureas have poor solubility. Haga at col. 26, ll. 3-4, Compound 53. It was further known that nicotinamide and picolinamide have high solubility in water. N-methyl picolinamide, an obvious derivative of picolinamide, would be an obvious adduct to Miller's Compound 102, which could be used by one of ordinary skill in the art to enhance the solubility of a raf inhibitor while maintaining its potency as a raf kinase inhibitor and improving binding in the enzyme receptor pocket. Accordingly, incorporating N-methylcarboxamide into Miller's Compound 102 would enhance solubility of Miller's Compound 102 resulting in better bioavailability and also enhanced binding to the enzyme receptor pocket. The enhanced solubility provided by incorporating N-methylcarboxamide into the heteroaryl phenyl group would result in the sorafenib structure. The resulting sorafenib structure is illustrated below:

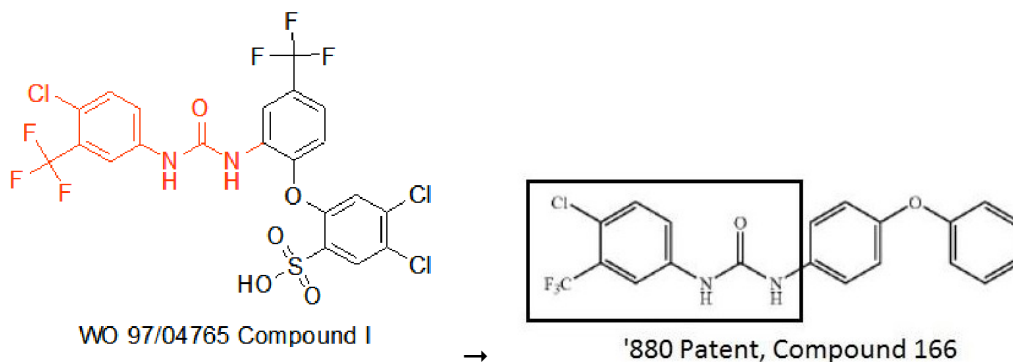


Accordingly, claim 1 is invalid under 35 U.S.C. § 103(a) as obvious in view of the prior art of Winkler, the Miller '265 publication and solubility optimization provided by N-methylcarboxamide of N-methyl picolinamide.

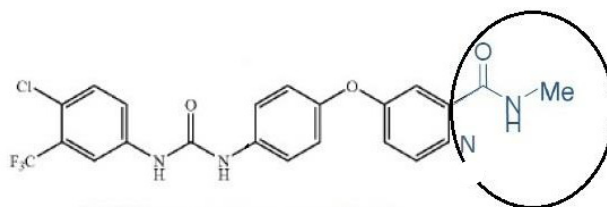
iv. **Claim 1 is Obvious in View of the Prior Art of Winkler, the Miller '880 Patent and Solubility Optimization**

1. **Selection of Lead Compound**

The selection of Winkler's ureido Compound I^a was discussed above. Compound 166 in Table 5 of the Miller '880 patent is the only Miller ureido compound that has trifluoromethyl and chloro moieties on one of its phenyl groups, a structure similar to Winkler's Compound I^a as illustrated directly below:



Compound 166 has the same backbone structure (indicated by the box) as Winkler's compound I^a and also as sorafenib as recited in claim 1 of the '834 patent. By comparison to sorafenib, Compound 166 is missing an N-methylpicolinamide moiety on a pyridine ring (in the circle) as shown below:

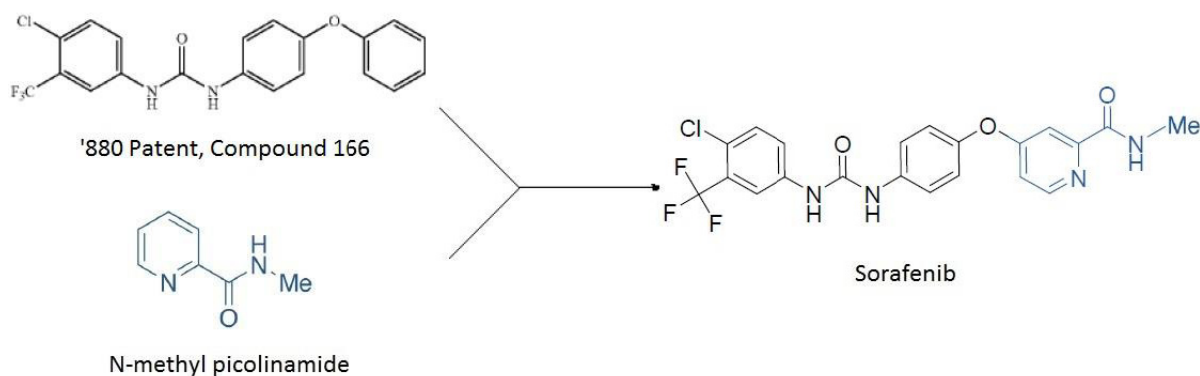


'880 Patent, Compound 166

The '834 patent has the same backbone structure. For example, the backbone of the '834 patent is A-D-B, wherein D is -NH-C(O)-NH-, A is a substituted moiety of up to 40 carbon atoms, and B is a substituted or unsubstituted, up to tricycle aryl or heteroaryl moiety of up to 30 carbon atoms. '834 patent at col. 2, ll. 15-17, ll. 26-28. Further, 2-(N-methylcarbamoyl)chloropyridine as disclosed in the Miller '880 patent is the same compound as 4-chloro-2-pyridinecarboxamide used in the '834 patent in the synthesis of sorafenib or compound 42 disclosed at col. 49, ll. 24-28 of the '834 patent. Thus, to design a ureido compound with anti-cancer activity, one of ordinary skill in the art would find it obvious to make sorafenib by using Winkler's Compound I^a to select Miller's Compound 166.

2. **Enhanced Solubility and Improved Binding in the Enzyme Receptor Binding as the Reason for Modifying Compound 166 as Disclosed in the Miller '880 Patent**

It was also known since at least September 5, 1989 that diphenyl ureas have poor solubility. (Haga, Compound 53 and Col. 26, ll. 3-4) It was further known that nicotinamide and picolinamide have high solubility in water. N-methyl picolinamide, an obvious derivative of picolinamide, would be an obvious adduct to Compound 166, which could be used by one of ordinary skill in the art to enhance the solubility of a anti-cancer drug while maintaining its potency and improving binding in an enzyme receptor pocket. Accordingly, incorporating N-methylpicolinamide into Compound 166 would enhance its solubility resulting in better bioavailability and also enhanced binding to the enzyme receptor pocket. The enhanced solubility provided by incorporating N-methylpicolinamide would result in the sorafenib structure. The resulting sorafenib structure, which has the N-methyl picolinamide shown in blue, is illustrated below:



Accordingly, claim 1 is invalid under 35 U.S.C. § 103(a) as obvious in view of the prior art of Winkler, the Miller '880 patent and solubility optimization provided by N-methyl picolinamide.

v. Obvious To Try

The modifications of Winkler-Haga or Winkler-Armistead, Winkler-Miller '265 publication, Winkler-Miller '880 patent to make sorafenib would be obvious to try to a person to a person of ordinary skill in the art. Therefore, claim 1 of the '834 patent is invalid.

In *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398 (2007), the U.S. Supreme Court articulated scenarios in which "obvious to try" is enough to defeat patentability under 35 U.S.C. § 103:

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

Id. at 420.

"Obvious to try" as articulated in KSR is also applicable to sorafenib. As discussed above, both the Miller '265 publication and the Miller '880 patent disclosed N-methylcarbamoyl substituted pyridines used in the preparation of sorafenib. As discussed above, in connection with at least the Miller '265 publication, the inventors were familiar with combinatorial methods of synthesis of diphenyl ureas using triphosgene, which was similar to a method of preparing sorafenib disclosed in the '834 patent. Therefore, the inventors of the '834 patent were familiar with combinatorial methods of synthesis for the development of a library of potential lead compounds whose structure-activity relationship (SAR) could be further explored vis-à-vis their anti-cancer potency and these compounds could be routinely optimized. Miller '265 publication,

para. [0185]. Further, the desire to provide drug-like lead compounds having increased solubility while preserving anti-cancer potency and increasing its enzyme binding ability, as described in Lipinski and Curatolo discussed above, provides a motivation and reasonable expectation of success for adding N-picolinamide on the hybrid structures discussed above or adding an N-methyl carbamoyl moiety on the pyridine ring of Miller's Compounds 102 or 166 as taught by Data from SRC PhysProp Database for N-methyl picolinamide.

vi. Admissions by Inventors in Later Publications and in the '834 Patent

Admissions by inventors in later publications further show that the development of sorafenib was the result of routine optimization and thus not inventive. For example, in Khire's publication discussed above, which was authored by many of the inventors of the '834 patent, these inventors describe how their knowledge and use of combinatorial chemistry led to the routine "optimization" of the lead compound which led to a series of potent, orally active raf-1 kinase inhibitors and that this culminated in the identification of a clinical candidate BAY 43-9006, which is sorafenib.

Other co-inventors of the '834 patent, namely Lowinger, Dumas and Smith authored another publication with Wilhelm, also discussed above, in which they acknowledge that in 1994, when a team was assembled to develop sorafenib, the introduction and refinement of *in vitro* HTS and combinatorial chemistry greatly facilitated the development of new chemicals. Moreover, an assay for HTS identification of selective Raf/MEK/ERK enzyme inhibitors discovered by Glaxo-Wellcome was vital in identifying and selecting candidate raf kinase inhibitors for further evaluation for Phase I clinical trials. Against this background, using HTS, ADME and known assay technologies to determine toxicology of various asymmetric ureas known as raf kinase inhibitors, the selection of Miller's Compound 102 as a lead compound and modifying it with an N-methyl picolinamide would have been obvious to try, and mere routine optimization as acknowledged by the inventors in the Wilhelm and Khire publications.

Even in the '834 patent, the Applicants stated that "[t]he activity of a given compound to inhibit raf kinase can be *routinely assayed*, e.g., according to procedures disclosed below." '834 patent, col. 9, ll. 43-45. Accordingly, sorafenib as claimed in claims 1, 2, 4, 5, 24, 25, 28, 29, 31 and 35-39 would have been obvious and therefore invalid over a combination of Miller's Compound 102 and 2-pyridine carboxamide as it would be obvious to screen these compounds at the time of the alleged invention to test their raf kinase activity, as it would be routine optimization.

vii. Secondary Considerations

There is no evidence of secondary considerations currently known that would successfully rebut a *prima facie* case of obviousness.

viii. Claims 2, 4, 5, 19, 24, 25, 28, 29, 30, 31 and 35-39 Are Invalid Under 35 U.S.C. § 103(a)

Claims 2, 4, 5, and 19 are dependent directly or indirectly on and incorporate the limitations of claim 1 and cover sorafenib at least as a specie. Accordingly, as discussed with respect to claim 1, these claims are invalid under 35 U.S.C. § 103(a) as obvious over the prior art of (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent) in combination with N-methyl picolinamide for the same reasons as discussed above with respect to claim 1.

Independent claims 24, 25, 35 and 39 recite sorafenib generically or as a specie. Accordingly, as discussed with respect to claim 1, these claims are invalid under 35 U.S.C. § 103(a) as obvious over the prior art of (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent in combination with N-methyl picolinamide for the same reasons as discussed above with respect to claim 1.

Claims 28, 29, and 36-38 are dependent from independent claims 24, 25 and 35, respectively and incorporate the limitations of claim 1 and recite sorafenib at least as specie. Accordingly, as discussed with respect to claim 1, these claims are invalid under 35 U.S.C. § 103(a) as obvious over the prior art of (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent in combination with N-methyl picolinamide for the same reasons as discussed above with respect to claim 1.

ix. Claims 30, 31, 32 and 40 Are Invalid Under 35 U.S.C. § 103(a)

Claims 30, 31, 32 and 40 depend from independent claims 1, 24, 25 and 39, respectively, and incorporate the limitations of these independent claims. Moreover, these claims also recite a pharmaceutically acceptable salt which is a) a basic salt of an organic or inorganic acid of a group including, among others, hydrochloric acid, hydrobromic acid and the like, or b) an acid salt of an organic or inorganic base containing an alkali metal cation and the like. Armistead teaches pharmaceutically acceptable salts of his compounds including those derived from pharmaceutically acceptable inorganic and organic acids, also including both acid salts and basic salts. Armistead at 29. "[W]hen, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is anticipated or obvious if one of them is taught in the prior art." *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (citing *In re Petering*, 301 F.2d 676, 682, 133 USPQ 275, 280 (CCPA 1962)) (emphasis in original). Accordingly, as discussed above, (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent in combination with N-methyl picolinamide in further view of Armistead would render obvious a pharmaceutically acceptable salt of sorafenib which is a) a basic salt of an organic or inorganic acid of a group including, among others, hydrochloric acid, hydrobromic

acid and the like, or b) an acid salt of an organic or inorganic base containing an alkali metal cation and the like and thus invalidates claims 30, 31, 32 and 40.

x. Claim 41 is Invalid Under 35 U.S.C. § 103 (a)

Claim 41 recites the tosylate salt of sorafenib. Armistead teaches antiproliferative ureido compounds and their pharmaceutically acceptable salts derived from pharmaceutically acceptable inorganic and organic acids also including tosylate. Armistead at 29. Pharmaceutically acceptable salts of Armistead's compounds include salts of inorganic or organic acids, e.g., *inter alia*, acetate, maleate, as well as tosylate and base salts, e.g., alkaline metal salts and the like. *Id.* One of ordinary skill in the art, seeking to provide pharmaceutically acceptable salts of organic acids of the sorafenib compound as taught by (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent in combination with N-methyl picolinamide would produce the tosylate salt of Armistead as part of routine optimization based on a reasonable expectation of success. Therefore, making an active into a particular salt form such as tosylate is not inventive as it does not have any effect on its therapeutic efficacy. *See, Pfizer Inc. v. Apotex Inc.*, 480 F.3d 1348 (Fed. Cir. 2007). In this case, the Federal Circuit concluded that "the optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious whereas here the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt." Cf. *In re Geisler*, 116 F.3d 1465, 1470 (Fed.Cir.1997) ("[I]t is not inventive to discover the optimum or workable ranges by routine experimentation" (quoting *Aller*, 220 F.2d at 456)); *In re Kulling*, 897 F.2d 1147, 1149 (Fed.Cir.1990).

Armistead disclosed a tosylate as a known pharmaceutical salt of antiproliferative ureido compounds. One of ordinary skill in the art would find it obvious and have a reasonable expectation of success in producing the tosylate of sorafenib as taught by (i) Winkler in view of Haga ; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with N-methyl picolinamide in further view of Armistead.

B. U.S. Patent No. 7,897,623

i. Claim 1 is Obvious in View of Winkler, Haga and Solubility Optimization

Claim 1 of the '623 would be obvious in *view* of Winkler, Haga, and solubility optimization for the reasons explained in Section IX.A.i.

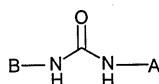
ii. Claim 1 is Obvious in View of the Prior Art of Winkler, Armistead and Solubility Optimization

Claim 1 of the '623 would be obvious in *view* of Winkler, Armistead, and solubility optimization for the reasons explained in Section IX.A.ii.

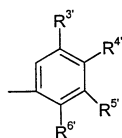
iii. Claim 1 is Obvious in View of the Prior Art of Winkler, the Miller '265 Publication and Solubility Optimization

Claim 1 of the '623 would be obvious in *view* of Winkler, the Miller '265 Publication, and solubility optimization for the reasons explained in Section IX.A.iii.

In addition, like the '623 patent, the Miller '265 publication describes symmetrical and unsymmetrical substituted diphenyl ureas useful for the inhibition of raf kinase. Like the '623 patent (Col. 2, ll. 6-7), Miller's aryl ureas include both aryl and heteroaryl analogues, which inhibit the raf pathway (Miller '265 publication, para. [0004]). Both types of ureas have the same structural backbone. Miller's ureas are illustrated as formula II:



wherein, A can be a six member ring having the structure below



Miller '265 publication at [0020] & [0021].

B can be substituted or unsubstituted, up to tricyclic aryl or heteroaryl moieties of up to 30 carbon atoms with at least one 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, where B is substituted, it is substituted by one or more substituents selected from the group consisting of halogen, up to per-halo, and W_n, wherein n is 0-3 and W is independently selected from many other groups. Miller '265 publication at [0022].

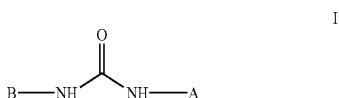
The '623 patent has the same backbone structure. For example, the backbone of the '623 patent is A-D-B, wherein D is -NH-C(O)-NH-, A is a substituted moiety of up to 40 carbon atoms, and B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms. ('623 patent, Col. 5, ll. 34-36, ll. 44-48)

In methods A16 and A20, the Miller '265 publication discloses carbamoyl substituted compounds useful for synthesis of substituted anilines (method A16) and 2-(N-methylcarbamoyl)pyridines (method A20). (Miller '265 publication, paras. [0151], [0152];[0161], [0162]) 2-(N-methylcarbamoyl) chloropyridine disclosed by Miller at para. [0162] is the same compound as 4-chloro-2-pyridinecarboxamide used in the '623 patent in the synthesis of sorafenib or compound 42 disclosed at Col. 49, ll. 24-28 of the '623 patent. The Miller '265 publication also discloses a combinatorial method for synthesis of diphenyl ureas using triphosgene which is similar to a method utilized in the '623 patent for the same purpose. (Miller '265 publication at para. [0185] and '623 patent at Col. 39, ll. 20 et seq.).

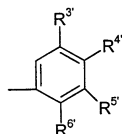
iv. **Claim 1 is Obvious in View of the Prior Art of Winkler, the Miller '880 Patent and Solubility Optimization**

Claim 1 of the '623 would be obvious in view of Winkler, the Miller '880 patent, and solubility optimization for the reasons explained in Section IX.A.iv.

Specifically, like the Miller '265 publication, the Miller '880 patent teaches the ureas disclosed in the Miller '880 patent are illustrated as formula I:



wherein, A can be a six member ring having the structure below



B can be substituted or unsubstituted, up to tricyclic aryl or heteroaryl moieties of up to 30 carbon atoms with at least one 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, where B is substituted, it is substituted by one or more substituents selected from the group consisting of halogen, up to per-halo, and W_n, wherein n is 0-3 and W is independently selected from many other groups. Miller '880 patent at col. 5, ll. 25 – 62. These ureas can be used to inhibit p38 kinase and also raf kinases. Miller '880 patent at col. 18, ll. 11-12.

The '623 patent has the same backbone structure. For example, the backbone of the '623 patent is A-D-B, wherein D is -NH-C(O)-NH-, A is a substituted moiety of up to 40 carbon atoms, and B is a substituted or unsubstituted, up to tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms. '623 patent at col. 5, ll. 34-36, ll. 44-48. In the 5 tables of the Miller '880 patent, all compounds are listed as displaying IC₅₀ inhibitory concentration between 1 nM and 10 μM for raf kinase. Miller '880 patent at col. 97, ll. 1-2.

Like the Miller '265 publication, the Miller '880 patent discloses carbamoyl substituted compounds useful for synthesis of substituted anilines (method A16) and 2-(N-methylcarbamoyl)pyridines (method A20). Miller '880 patent at col. 42, ll. 1-34; Col. 44, ll. 15-51) 2-(N-methylcarbamoyl)chloropyridine disclosed in the Miller '880 patent is the same compound as 4-chloro-2-pyridinecarboxamide used in the '623 patent in the synthesis of sorafenib or compound 42 disclosed at Col. 49, ll. 24-28 of the '623 patent.

v. Obvious to Try

The modifications of Winkler-Haga or Winkler-Armistead, Winkler-Miller '265 publication, Winkler-Miller '880 patent to make sorafenib were obvious to try and, therefore, claim 1 of the '623 patent is invalid. The reasons are provided in Section IX.A.v, which are hereby incorporated by reference.

vi. Admissions by Inventors in Later Publications and in the '623 Patent

Admissions by inventors in later publications further show that the development of sorafenib was the result of routine optimization and thus not inventive. For example, in Khire's publication discussed above, which was authored by many of the inventors of the '623 patent, these inventors describe how their knowledge and use of combinatorial chemistry led to the routine "optimization" of the lead compound which led to a series of potent, orally active Raf-1 kinase inhibitors and that this culminated in the identification of a clinical candidate BAY 43-9006, also known as sorafenib.

Other co-inventors of the '623 patent, namely Lowinger, Dumas and Smith authored another publication with Wilhelm, also discussed above, in which they acknowledge that in 1994, when a team was assembled to develop sorafenib, the introduction and refinement of *in vitro* HTS and combinatorial chemistry greatly facilitated the development of new chemicals. Moreover, an assay for HTS identification of selective Raf/MEK/ERK enzyme inhibitors discovered by Glaxo-Wellcome was vital in identifying and selecting candidate Raf kinase inhibitors for further evaluation for Phase I clinical trials. Against this background, using HTS, ADME and known assay technologies to determine toxicology of various asymmetric ureas known as raf inhibitors, the selection of Miller's Compound 102 as a lead compound and modifying it with an N-methyl picolinamide would have been obvious to try and mere routine optimization as acknowledged by the inventors in the Wilhelm and Khire publications.

Further, as Applicants admitted in the '623 patent, since inhibition against raf kinase lead to inhibition against p38 kinase, testing sorafenib's anti-cancer potency by inhibiting p38 kinase was a matter of routine experimentation. '623 patent at col. 14, ll. 31-33.

Nevertheless, since claim 1 of the '623 patent does not recite any activity, selecting Miller's Compound 102 based on its anti-cancer potency as a raf kinase inhibitor conforms with at least one of sorafenib's potencies. Further, as discussed above, Armistead discloses pharmaceutically acceptable carriers. Armistead at 34. Accordingly, sorafenib as claimed in claim 1 of the '623 patent would have been obvious to one of ordinary skill in the art and therefore claim 1 is invalid over a combination of Miller and what was known about 2-pyridine carboxamide in further view of Armistead.

vii. Secondary Considerations

There is no evidence of secondary considerations currently known that would successfully rebut a *prima facie* case of obviousness.

viii. Claims 2-8 Are Invalid Under 35 U.S.C. §103(a)

Claim 2 depends from claim 1 and in addition requires that the pharmaceutically acceptable salt is tosylate. Armistead teaches antiproliferative ureido compounds and their pharmaceutically acceptable salts derived from pharmaceutically acceptable inorganic and organic acids also including tosylate. Armistead at 29. Pharmaceutically acceptable salts of Armistead's compounds include salts of inorganic or organic acids, e.g., *inter alia*, acetate, maleate, as well as tosylate and base salts, e.g., alkaline metal salts and the like. *Id.* One of ordinary skill in the art, seeking to provide pharmaceutically acceptable salts of organic acids of the sorafenib compound as taught by (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent in combination with N-methyl picolinamide would produce the tosylate salt of Armistead as part of routine optimization based on a reasonable expectation of success. Therefore, making an active into a particular salt form such as tosylate is not inventive as it does not have any effect on its therapeutic efficacy. *See, Pfizer Inc. v. Apotex Inc.*, 480 F.3d 1348 (Fed. Cir. 2007). In this case, the Federal Circuit concluded that "the optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious whereas here the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt." Cf. *In re Geisler*, 116 F.3d 1465, 1470 (Fed.Cir.1997) ("[I]t is not inventive to discover the optimum or workable ranges by routine experimentation" (quoting *Aller*, 220 F.2d at 456)); *In re Kulling*, 897 F.2d 1147, 1149 (Fed.Cir.1990).

Armistead disclosed a tosylate as a known pharmaceutical salt of antiproliferative ureido compounds, one of ordinary skill in the art would find it obvious and have a reasonable expectation of success in producing the tosylate of sorafenib as taught by (i) Winkler in view of

Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with N-methyl picolinamide in further view of Armistead.

Claim 3 recites a pharmaceutical composition comprising sorafenib or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. As discussed above, Winkler or Armistead disclose a physiologically acceptable carrier such as sodium chloride or sterile aqueous carrier among their pharmaceutically acceptable carriers. Accordingly, claim 3 is invalid under 35 U.S.C. § 103(a) as rendered obvious by (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with N-methyl picolinamide or in further view of Armistead.

Claim 4 depends from claim 3 and further requires that the pharmaceutically acceptable salt is a tosylate salt. Accordingly, as discussed above in connection with claim 2, claim 4 is invalid as obvious over (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with N-methyl picolinamide in further view of Armistead.

Claim 5 recites a tablet comprising sorafenib or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient. As discussed above, Winkler, Haga, Armistead, the Miller '265 publication or the Miller '880 patent, all disclose utilizing their compounds in tablets, with pharmaceutically acceptable excipients including diluents. Accordingly, claim 5 is invalid as obvious over (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with N-methyl picolinamide.

Claim 6 depends from claim 5 and further requires that the pharmaceutically acceptable salt is a tosylate salt. Accordingly, as discussed above in connection with claims 2 and 4, claim 6 is invalid as obvious over (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with N-methyl picolinamide in further view of Armistead.

Claim 7 depends from claim 5 and further requires that the pharmaceutically acceptable excipient be a diluent, granulating agent, disintegrating agent or a binding agent. As discussed above in connection with claim 5, claim 7 is invalid as obvious over (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with N-methyl picolinamide.

Claim 8 depends from claim 6 and further requires that the pharmaceutically acceptable excipient be a diluent, granulating agent, disintegrating agent or a binding agent. Accordingly, as discussed above in connection with claims 2, 4, and 6, claim 8 is invalid as obvious over (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the

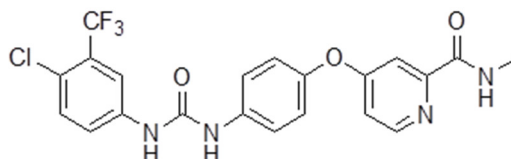


CONFIDENTIAL
November 9, 2015
Page 91

Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with N-methyl picolinamide.

C. U.S. Patent No. 7,235,576

Claim 1 is an independent, Markush style claim, reciting, among others compound N-(4-chloro-3-(trifluoromethyl)phenyl)-N'-(4-(2-(N-methylcarbamoyl)-4-pyridyloxy)phenyl)urea or sorafenib of the formula:



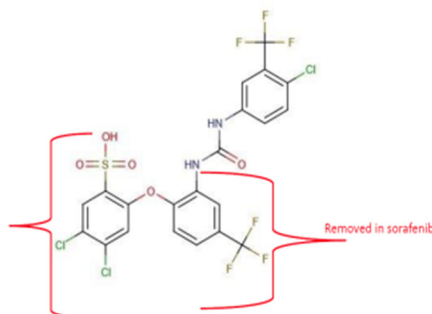
As set forth in the Certificate of Correction, claims 5, 8, 11 and 14 are also independent Markush style claims directed to a pharmaceutically acceptable salt of a compound selected from a group consisting of 4 compounds (claim 5), 3 compounds (claims 8 and 11) and 2 compounds (claim 14), of which one compound in the list is sorafenib.

When analyzing the validity or invalidity of Markush style claims, it has recognized that "[t]he novelty and nonobviousness of a claim with a Markush group is determined much as in the case of other generic claims. If an applicant claims an invention with an element defined as a Markush group of A, B, C, and D, and the prior art discloses the combination with element D, then the claim is invalid. Similarly, if the prior art renders the combination with element D obvious to one with ordinary skill in the relevant art, then the claim is invalid under Section 103." *Chisum* §8.06[2][f], *Ecolochem, Inc. v. Southern California Edison Co.*, 863 F. Supp. 1165 (C.D. Cal. 1994), *aff'd in part, rev'd in part*, 91 F.3d 169 (Fed. Cir. 1996) (unpublished table decision) (MICHEL, Newman, Clevenger), *aff'd in part, rev'd in part after remand*, 227 F.3d 1361 (Fed. Cir. 2000) (MICHEL, Clevenger, Rader), *cert. denied*, 121 S. Ct. 1607 (2001). Accordingly, if the sorafenib specie is obvious in view of the prior art, claims 1, 5, 8, 11 and 14 which recite sorafenib as a specie would also be invalid for obviousness as well.

i. Claims 1, 5, 8, 11 and 14 Are Obvious in View of the Prior Art of Winkler, Miller PCT and Solubility Optimization

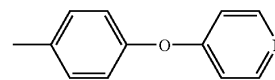
1. Selection of Lead Compound

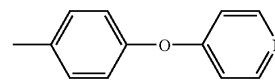
Winkler teaches ureido compounds, which have antiproliferative properties against cancer cells. Of note, sorafenib is a ureido compound having a trifluoromethyl and a chloro moiety on one of its phenyl groups. Winkler prefers Compound I^a, a ureido compound having a trifluoromethyl moiety and a chloro moiety, which has improved antiproliferative properties against cancer. Compound I^a of Winkler is the ureido compound shown below:



Like the '576 patent which has the field of invention and the background of invention identical to that of Miller PCT, in the summary of the invention, Miller's compounds, just like those in the '576 patent, are inhibitors of the raf kinase pathway. Miller discloses the p21^{ras} oncogene, a major contributor to the development and progression of human solid cancers, and that inhibiting raf kinase results in inhibiting active ras and thus, the inhibition of the growth of a variety of tumors. (Miller PCT, page 2, ll. 6-17) Like in the '576 patent (Col. 1, l. 66 to Col. 2, l. 1), Miller PCT's aryl ureas include both aryl and heteroaryl analogues, which inhibit the raf pathway. Miller PCT at 2. Both types of ureas have the same structural backbone.

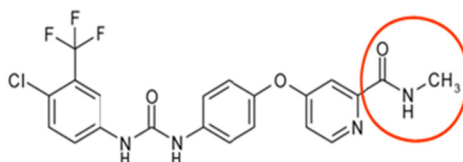
Miller discloses Compound 102, which is a structure very similar to sorafenib except that it is missing an N-methylcarbamoyl moiety on the pyridine ring. Miller lists 22 structures



similar to Winkler's Compound I^a. However, based on R2 of , tested in every compound permutation of Tables 1 and 2 of Miller, Compound 102 emerges as the natural lead compound.

The selection of Winkler's ureido Compound I^a was discussed above. The further selection of Miller's Compound 102 in Miller's Table 3 based on Winkler's Compound I^a was also discussed above. Miller's Compound 102 also has the same backbone structure as sorafenib that is claimed in claims 1, 5, 8, 11 and 14 of the '576 patent. For example, the backbone of the '576 patent is A-D-B, wherein D is -NH-C(O)-NH-, A is a substituted moiety of up to 40 carbon atoms, and B is a substituted or unsubstituted, to a tricyclic aryl or heteroaryl moiety of up to 30 carbon atoms with at least one 6-member cyclic structure bound directly to D containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur. '576 patent at col. 2, ll. 10-12, ll. 21-25.

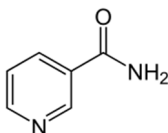
By comparison to sorafenib, Miller PCT's Compound 102 is missing an N-methylcarbamoyl moiety as shown encircled below:



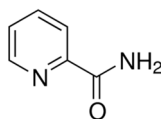
Miller's Compound 102 has more than a mere structural similarity to sorafenib; it is recognized as a potent raf kinase inhibitor having an IC_{50} of between 1 nM and 10 μ M. Miller at 74, l. 20. When the claimed invention and structurally similar prior art species share any useful property, that will generally be sufficient to motivate an artisan of ordinary skill to make the claimed species. *In re Dillon*, 919 F.2d 688, 711 (Fed. Cir. 1990) (*en banc*). Further, Miller PCT also discloses a combinatorial method for synthesis of diphenyl ureas using triphosgene which is similar to a method utilized in the '576 patent for the same purpose. Miller PCT at 59; '576 patent at col. 35, ll. 50 et seq. Accordingly, Winkler in view of Miller PCT in combination with picolinamide/N-methyl picolinamide would render obvious sorafenib and thus invalidate all claims that recite it as a specie, namely claims 1, 5, 8, 11 and 14 of the '576 patent.

2. **Enhanced Solubility and Improved Binding in the Enzyme Receptor Binding as Reason or Motivation for Modifying Miller's Compound 102**

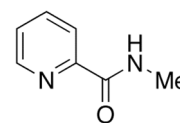
It was also known since at least September 5, 1989 that diphenyl ureas have poor solubility. (Haga, Compound 53 and Col. 26, ll. 3-4). It was also known since at least 1996, that nicotinamide and picolinamide have high solubility in water, 5×10^5 mg/L and 1.8×10^5 mg/L, respectively (data from SRC PhysProp Database)



Nicotinamide



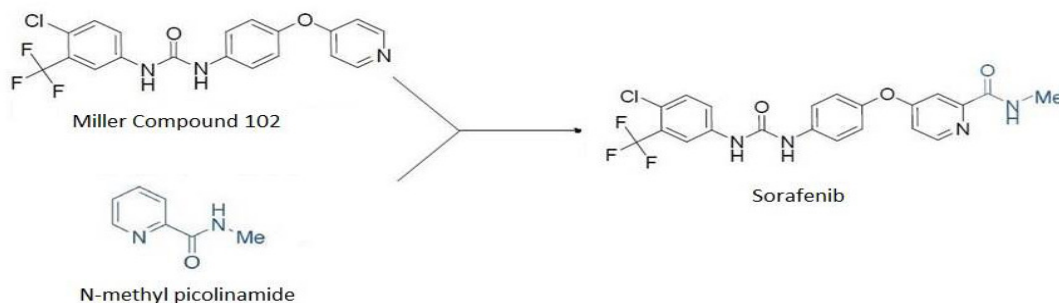
Picolinamide



N-methyl picolinamide

2-pyridine carboxamide or N-methyl picolinamide is an obvious derivative of picolinamide, which one of skill in the art seeking to enhance the solubility of a raf kinase inhibitor while maintaining its potency as a raf kinase inhibitor and improving binding in the enzyme receptor pocket, as disclosed by Lipinski above, would find it obvious to incorporate the N-methylcarboxamide structure into Miller PCT's Compound 102.

Specifically, to design a ureido compound to treat cancer, one of ordinary skill in the art would find it obvious to make sorafenib by using Winkler's Compound I^a to select Miller's Compound 102 and optimize it for increased solubility with the N-methyl carbamoyl group knowing that N-methyl picolinamide enhances solubility of a compound, and one of ordinary skill in the art would arrive at sorafenib as illustrated below:

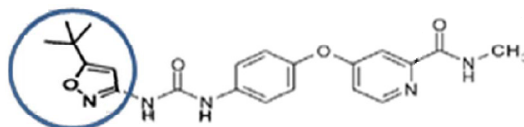


Accordingly, incorporating N-methylcarboxamide into Miller PCT's Compound 102 would enhance solubility of Compound 102 resulting in better bioavailability and also enhanced binding to the enzyme receptor pocket. Miller PCT also discloses pharmaceutically acceptable salts of his compounds, so that a pharmaceutically acceptable salt of sorafenib is obvious in the prior art and thus, claims 1, 5, 8, 11 and 14 are invalid as obvious under 35 U.S.C § 103 over Miller PCT in view of N-methyl picolinamide solubility.

ii. **Claims 1, 5, 8, 11 and 14 Are Obvious in View of the Miller PCT, Dumas and Solubility Optimization**

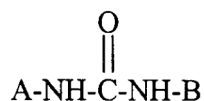
In Compound 101, Dumas describes an anti-cancer raf kinase inhibitor that has the same structure as sorafenib as claimed in the '576 patent, except that Dumas' raf kinase inhibitor contains a 5-substituted-3-isoxazolyl group in lieu of a 2-chloro-5-(trifluoromethyl)phenyl substituent at the B position of the sorafenib A-D-B backbone.

As explained above, the structure of Dumas' Compound 101 is similar to sorafenib except that instead of a 2-chloro-5-(trifluoromethyl)phenyl substituent at the B position of the A-D-B backbone, Dumas has a 5-tert-butyl-3-isoxazolyl group shown above in a circle.



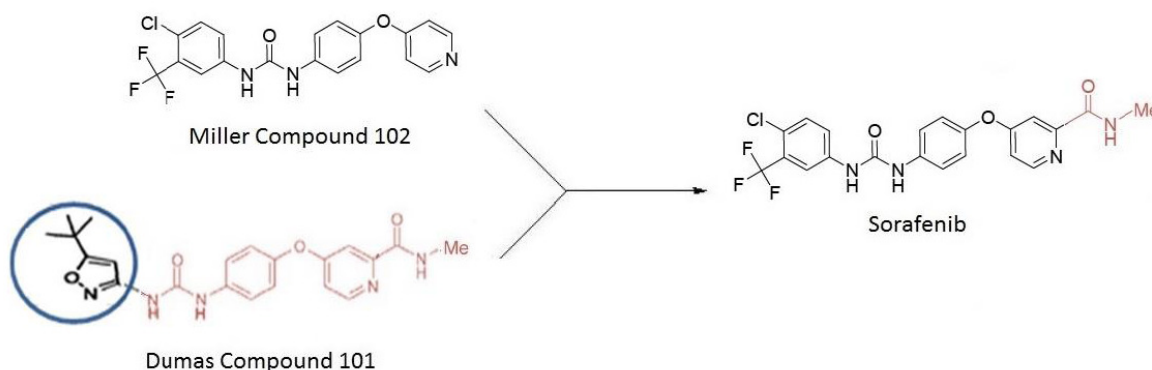
As in Miller PCT and the '576 patent, Dumas' compounds are asymmetrical substituted diaryl ureas that are useful to treat cancers by inhibiting raf kinase. In particular, as described in the '576 patent (Col. 1, l. 66 to Col. 2, l. 1) and Miller's aryl ureas, Dumas' aryl ureas include both aryl and heteroaryl analogues, which inhibit the raf pathway (Dumas, page 2, ll. 21-26) and are useful in treating solid cancers such as, for example, carcinomas (e.g., lungs, pancreas, thyroid, bladder or colon, myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma). Dumas at 2.

Both Dumas' ureas and those recited in claim 1 of the '576 patent have the same structural backbone. Dumas' ureas are illustrated on page 2 as formula I:



wherein B is generally an unsubstituted or substituted, up to tricyclic, aryl or heteroaryl moiety with up to 30 carbon atoms with at least one 5 or 6 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur. Further, 2-(N-methylcarbamoyl)chloropyridine disclosed by Dumas on page 55 is the same compound as 4-chloro-2-pyridinecarboxamide used in the '576 patent in the synthesis of sorafenib or compound 42 disclosed at Col. 46, ll. 15-20 of the '576 patent.

Since both Miller's Compound 102 and Dumas' Compound 101 have not only very similar activity and are structurally similar, but also have many common co-inventors, and Dumas teaches the efficacy of the carbamoyl substituent⁴ with respect to raf kinase inhibitory potency, one of ordinary skill in the art would be motivated to modify Miller's Compound 102 with Dumas' Compound 101 to produce the claimed sorafenib compound as illustrated below:



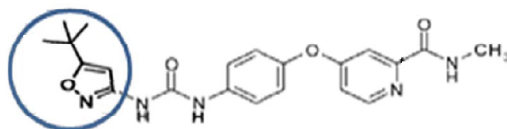
The fact that both compounds Miller PCT's Compound 102 and Dumas' Compound 101 are potent raf kinase inhibitors, provides the motivation for modifying Miller PCT's Compound 102 with the N-methyl carbamoyl moiety present in Dumas' Compound 101 to produce sorafenib as the skilled artisan would want to produce a potent raf kinase inhibitor. Accordingly, as discussed above, Miller PCT in combination with picolinamide/N-methyl picolinamide or Miller PCT in combination with Dumas would render obvious sorafenib and thus invalidate all

⁴ At page 112, Dumas states that "[a]ll compounds exemplified displayed IC₅₀s of between 1 nM and 10 μM."

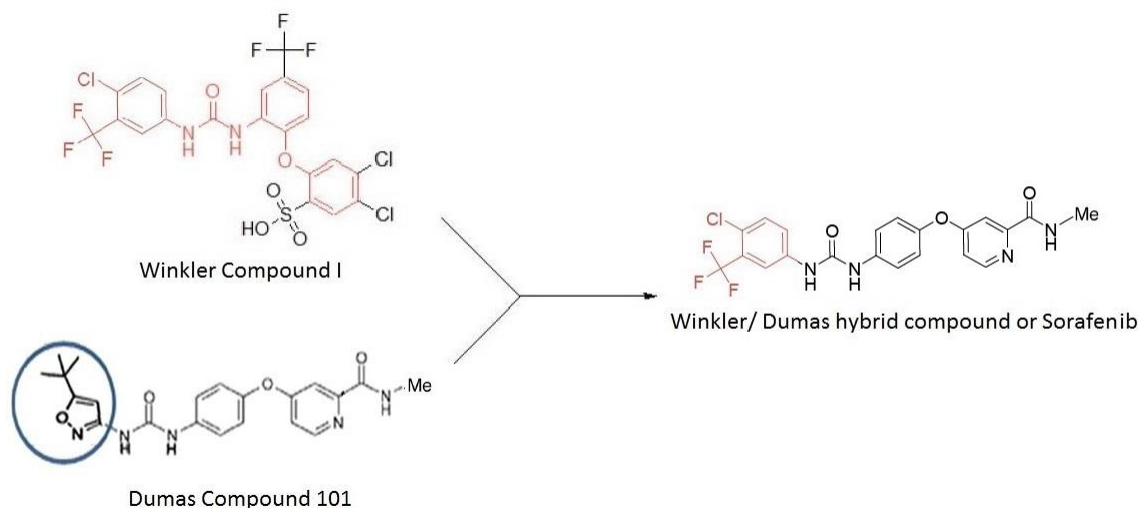
claims that recite it as a specie. Further, Dumas and Miller PCT also disclose pharmaceutically acceptable salts of their compounds, so that a pharmaceutically acceptable salt of sorafenib is obvious in the prior art and thus, claims 1, 5, 8, 11 and 14 are invalid as obvious under 35 U.S.C. § 103 over Miller PCT in combination with Dumas in view of N-methyl picolinamide solubility.

iii. Claims 1, 5, 8, 11 and 14 Are Obvious in View of the Prior Art of Winkler, Dumas and Solubility Optimization

The selection of Winkler's ureido Compound Ia was discussed above. The further selection of Dumas' Compound 101 in Dumas Table 1 based on Winkler's Compound I^a would be clear to a person of ordinary skill in the art. Dumas teaches Compound 101 as the closest structure to Winkler's Compound I^a. Like Winkler's Compound I^a, Dumas' Compound 101 has anti-cancer properties by inhibiting a raf kinase. Further, Dumas' Compound 101 contains an N-methyl carbamoyl moiety, which one of ordinary skill in the art would recognize as a compound of enhanced solubility. Based on Winkler's Compound I^a, Dumas' Compound 101 emerges as a natural lead compound for further investigation. Specifically, by further applying Winkler's backbone structure of diphenyl or diaryl urea, Compound 101 emerges as a preferred compound. In Compound 101, R2 does not have any other substituents on its rings other than methyl carbamoyl which enhances its solubility, and therefore it would be the best candidate for further consideration among the seven potential candidates listed in Table 1. As explained above, Dumas' Compound 101 has the same backbone structure as sorafenib that is claimed in claims 1, 5, 8, 11 and 14 of the '576 patent. By comparison to sorafenib, Dumas' Compound 101 is missing a 2-chloro-5-(trifluoromethyl)phenyl substituent at the B position of the A-D-B backbone where Dumas has a 5-tert-butyl-3-isoxazolyl group shown below in a blue color circle:



Thus, Dumas' Compound 101 can be selected as a lead compound for further investigation based on its similarity to Winkler's Compound I^a and because it contains an N-methyl carbamoyl moiety which one of ordinary skill in the art would find useful to improve the solubility of a Winkler-Dumas hybrid.



Dumas also discloses pharmaceutically acceptable salts of his compounds, so that a pharmaceutically acceptable salt of sorafenib is obvious in the prior art and thus, claims 1, 5, 8, 11 and 14 are invalid as obvious under 35 U.S.C. § 103 over Winkler in combination with Dumas in view of N-methyl picolinamide solubility.

iv. **Claims 1, 5, 8, 11 and 14 Are Obvious in View of the Prior Art of Winkler, Haga and Solubility Optimization**

Claims 1, 5, 8, 11, and 14 are obvious in view of Winkler, Haga, and solubility optimization for the same reasons explained in Section IX.A.i.

v. **Claim 1 is Obvious in View of the Prior Art of Winkler, Armistead and Solubility Optimization**

Claim 1 is obvious in view of Winkler, Armistead, and solubility optimization for the same reasons explained in Section IX.A.ii.

vi. **Obvious to Try**

The modifications of Winkler-Miller, Winkler-Miller-Dumas, Winkler-Dumas, Winkler-Haga or Winkler-Armistead to make sorafenib were obvious to try and, therefore, claims 1, 5, 8, 11 and 14 of the '576 patent are invalid. *KSR*, 550 U.S. 398 at 420. As discussed above, both Miller PCT and Dumas were familiar with combinatorial methods of synthesis of diphenyl ureas using triphosgene, which is similar to a method of preparing sorafenib disclosed in the '576 patent. Also as discussed above, both Miller PCT and Dumas disclosed N-methylcarbamoyl

substituted pyridines used in the preparation of sorafenib. Therefore, the inventors of the '576 patent were familiar with combinatorial methods of synthesis for the development of a library of potential lead compounds whose structure-activity relationship (SAR) could be further explored vis-à-vis their raf kinase inhibitory potency and these compounds could be routinely optimized. (Miller PCT, page 59, ll. 4-17 and Dumas, page 70, ll. 12-24.) Further, since the Miller PCT inventors were familiar with the N-methyl carbamoyl substituted pyridine of Dumas, and there were a finite number of compounds having raf kinase inhibitory potency (144 compounds disclosed in Miller PCT), when working on the compounds of the '576 patent, the inventors would have found it obvious to test the inhibitory activity towards raf kinase of Miller PCT's Compound 102 having the N-methyl carbamoyl moiety on the pyridine ring found in Dumas' Compound 101.

Further, the desire to provide drug-like lead compounds having increased solubility while preserving raf kinase inhibitory potency and increasing its enzyme binding ability, as described in Lipinski and Curatolo discussed above, provides a motivation and reasonable expectation of success for adding an N-methyl carbamoyl moiety on the pyridine ring of Miller PCT's Compound 102 as taught for N-methyl picolinamide or Dumas' Compound 101.

vii. Admissions by Inventors in Later Publications and in the '576 Patent

Admissions by inventors in later publications further show that the development of sorafenib was the result of routine optimization and thus not inventive. For example, in Khire's publication discussed above, which was authored by many of the inventors of the '576 patent, these inventors describe how their knowledge and use of combinatorial chemistry led to the routine "optimization" of the lead compound which led to a series of potent, orally active Raf-1 kinase inhibitors and that this culminated in the identification of a clinical candidate BAY 43-9006, which is sorafenib.

Other co-inventors of the '576 patent, namely Lowinger, Dumas and Smith authored another publication with Wilhelm, also discussed above, in which they acknowledge that in 1994, when a team was assembled to develop sorafenib, the introduction and refinement of *in vitro* HTS and combinatorial chemistry greatly facilitated the development of new chemicals. Moreover, an assay for HTS identification of selective Raf/MEK/ERK enzyme inhibitors discovered by Glaxo-Wellcome was vital in identifying and selecting candidate raf kinase inhibitors for further evaluation for Phase I clinical trials. Against this background, using HTS, ADME and known assay technologies to determine toxicology of various asymmetric ureas known as raf kinase inhibitors, the selection of Miller PCT's Compound 102 as a lead compound and modifying it with either a N-methyl picolinamide or Dumas' Compound 101 would have been obvious to try, and mere routine optimization as acknowledged by the inventors in the Wilhelm and Khire publications.

Even in the '576 patent, the applicants state that "[t]he activity of a given compound to inhibit raf kinase can be **routinely assayed**, e.g., according to procedures disclosed below."

(‘576 patent, Col. 9, ll. 47-49) Accordingly, sorafenib as claimed in claims 1, 5, 8, 11 and 14 would have been obvious and therefore invalid over a combination of Miller and 2-pyridine carboxamide or a combination of Miller’s Compound 102 and Dumas’ Compound 101 as it would be obvious to screen these compounds at the time to test their raf kinase activity as it would be routine.

viii. Secondary Considerations

There is no evidence of secondary considerations currently known that would successfully rebut a *prima facie* case of obviousness.

ix. Claims 2, 3, 5, 6, 9, 12, and 15 Are Invalid Under 35 U.S.C. § 103(a)

Claims 2, 3, 5, 6, 9, 12, and 15 are dependent directly or indirectly on and incorporate the limitations of claims 1, 5, 8, 11 and 14, respectively, and cover sorafenib as a specie while specifying that the pharmaceutically acceptable salt can be a basic salt of an organic or inorganic acid or an acid salt of an organic or inorganic base. As discussed with respect to claims 1, 5, 8, 11 and 14, these claims are invalid under 35 U.S.C. § 103(a) as obvious over the prior art of (i) Miller PCT in combination with N-methyl picolinamide; (ii) Miller PCT and Dumas in combination with N-methyl picolinamide; (iii) Winkler and Haga in combination with N-methyl picolinamide; or (iv) Winkler and Armistead in combination with N-methyl picolinamide for the same reasons as discussed above with respect to claims 1, 5, 8, 11 and 14. Moreover, as also discussed above, both Miller PCT, Dumas and Armistead disclose pharmaceutically acceptable salts which can be either basic or acid salts as recited in claims 2, 3, 5, 6, 9, 12, and 15. “[W]hen, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is anticipated or obvious if one of them is taught in the prior art.” *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (citing *In re Petering*, 301 F.2d 676, 682, 133 USPQ 275, 280 (CCPA 1962)) (emphasis in original) Accordingly, claims 2, 3, 5, 6, 9, 12, and 15 are invalid under 35 U.S.C. § 103(a) as obvious over the prior art of (i) Miller PCT in combination with N-methyl picolinamide; (ii) Miller PCT and Dumas in combination with N-methyl picolinamide; (iii) Winkler and Haga in combination with N-methyl picolinamide; or (iv) Winkler and Armistead in combination with N-methyl picolinamide for the same reasons as discussed above with respect to claims 1, 5, 8, 11 and 14.

x. Claims 4, 7, 10, 13, and 16 Are Invalid Under 35 U.S.C. § 103(a) Over Miller PCT In Combination With Picolinamide/N-Methyl Picolinamide or Miller PCT In Combination With Dumas Further In View of Armistead

Claims 4, 7, 10, 13, 16 are Markush style claims which recite, *inter alia*, the tosylate salt of sorafenib. Miller PCT, Dumas and Haga broadly recite many pharmaceutically acceptable salts as discussed above, however, they do not specifically disclose a tosylate salt of their compounds. As discussed above, Armistead discloses compounds which have anti-cancer

potency, the same activity as that of sorafenib. In particular, Armistead teaches antiproliferative ureido compounds and their pharmaceutically acceptable salts derived from pharmaceutically acceptable inorganic and organic acids also including tosylate. Armistead at 29, l. 16. Pharmaceutically acceptable salts of Armistead's compounds include salts of inorganic or organic acids, e.g., *inter alia*, acetate, maleate, as well as tosylate and base salts, e.g., alkaline metal salts and the like. Armistead at 29, ll. 1-28) One of ordinary skill in the art, seeking to provide pharmaceutically acceptable salts of organic acids of the sorafenib compound as taught by (i) Winkler in view of Miller PCT; (ii) Winkler in view of Miller PCT and Dumas; (iii) Winkler PCT in view of Dumas; (iv) Winkler in view of Haga; or (v) Winkler in view of Armistead in combination with N-methyl picolinamide would produce the tosylate salt of Armistead as part of routine optimization based on a reasonable expectation of success. Therefore, making an active into a particular salt form such as tosylate is not inventive as it does not have any effect on its therapeutic efficacy. *See, Pfizer Inc. v. Apotex Inc.*, 480 F.3d 1348 (Fed. Cir. 2007). In this case, the Federal Circuit concluded that "the optimization of the acid addition salt formulation for an active pharmaceutical ingredient would have been obvious whereas here the acid addition salt formulation has no effect on the therapeutic effectiveness of the active ingredient and the prior art heavily suggests the particular anion used to form the salt." Cf. *In re Geisler*, 116 F.3d 1465, 1470 (Fed.Cir.1997) ("[I]t is not inventive to discover the optimum or workable ranges by routine experimentation" (quoting *Aller*, 220 F.2d at 456)); *In re Kulling*, 897 F.2d 1147, 1149 (Fed.Cir.1990).

Armistead disclosed tosylate as a known pharmaceutical salt of antiproliferative ureido compounds, one of ordinary skill in the art would find it obvious and have a reasonable expectation of success in producing the tosylate of sorafenib as taught by (i) Winkler in view of Miller; (ii) Winkler in view of Miller and Dumas; (iii) Winkler in view of Dumas; (iv) Winkler in view of Haga; or (v) Winkler in view of Armistead in combination with N-methyl picolinamide. Accordingly, claims 4, 7, 10 and 13 are invalid under 35 U.S.C. § 103(a) as obvious over the prior art of (i) Winkler in view of Miller; (ii) Winkler in view of Miller and Dumas; (iii) Winkler in view of Dumas; (iv) Winkler in view of Haga; or (v) Winkler in view of Armistead in combination with N-methyl picolinamide would produce the tosylate salt of Armistead as part of routine optimization based on a reasonable expectation of success.

xi. Claim 17 Is Invalid Under 35 U.S.C. § 103

Claim 17 recites a pharmaceutical composition comprising a pharmaceutically acceptable salt of claims 1-15 or 16 and pharmaceutically acceptable carrier. A "pharmaceutically acceptable carrier," based on its ordinary meaning as understood in the art, would encompass a physiologically acceptable carrier. As discussed above, Miller PCT and Dumas disclose pharmaceutical compositions that include compounds described above and a physiologically acceptable carrier. Accordingly, claim 17 is invalid under 35 U.S.C. § 103(a) as obvious over the prior art of (i) Winkler in view of Miller PCT; (ii) Winkler in view of Miller PCT and Dumas; (iii) Winkler in view of Dumas; (iv) Winkler in view of Haga; (v) Winkler in view of Armistead in combination with N-methyl picolinamide.

D. U.S. Patent No. 8,877,933

One of ordinary skill in the art would be well motivated to search for and isolate polymorphic forms of sorafenib tosylate. Knowing that sorafenib tosylate was a pharmaceutically active compound that could be administered to patients in the treatment of various cancers (Carter), one of ordinary skill in the art would next turn to the routine process of isolating polymorphs of that substance. A standard step in the production of dosage forms of a new drug includes the isolation and characterization of polymorphic forms of the drug. Guillory at 184, 185. One of ordinary skill in the art would know that it was “essential” to isolate the thermodynamically stable form early in the formulation process. *Id.* at 184. Such efforts could be undertaken through numerous techniques as discussed extensively by Guillory. Those techniques include crystallization of polymorphs from a single solvent and thermal treatment of the isolated solid state compound. *Id.* at 185-202.

Indeed, several of the methods of obtaining polymorphic forms disclosed in Guillory were employed by the inventors of the '933 patent to obtain form I of sorafenib tosylate. The '933 patent discloses the following methods of producing polymorphic form I of sorafenib tosylate.

- Sorafenib tosylate Form II is placed in an inert solvent at room temperature until it is converted into sorafenib tosylate Form I. '933 patent at col.11, ll.48-53; *cf.* Guillory at 188.
- Sorafenib tosylate Form II is placed in an inert solvent, heated to reflux, cooled, and crystals of polymorphic form I are formed. '933 patent at col.11, ll.23-35; *cf.* Guillory at 189.
- Crystals of sorafenib tosylate Form II is heated from 195 to 222°C at a heating rate of 10 to 30°C/min, and subsequently cooling the composition to room temperature (10-30°C) at a cooling rate of 1°C to about 4°C. '933 patent at col.12, ll.54-62; *cf.* Guillory at 195-97.

Such efforts are not the product of innovation, but are rather steps followed in accord with standard and well-known approaches of isolating and characterizing polymorphs. *See KSR*, 550 U.S. at 421. Thus, one of ordinary skill in the art would be motivated to undertake the “essential” step of isolating thermodynamically stable polymorphs of sorafenib tosylate. To undertake this effort, that individual would have the enabling disclosure of Guillory, which provides methods of obtaining that thermodynamically stable polymorph. Under the relevant case law, the thermodynamically stable polymorph of sorafenib tosylate isolated by such efforts would be “the product not of innovation but of ordinary skill and common sense” and would be obvious under 35 U.S.C. § 103(a). *Zubin*, 561 F.3d at 1360 (quoting *KSR*, 550 U.S. at 421).

Further, data characterizing the obvious polymorphs of sorafenib tosylate – namely, the melting point and XRD, IR, and Raman spectra – are inherent properties of the obvious polymorph form I.

Each claim of the '933 patent is invalid as obvious for the following reasons:

i. Claims 1-4 Are Obvious In View of Guillory and Carter

One of skill in the art would employ the standard techniques disclosed in the enabling disclosure of Guillory to isolate the claimed thermodynamically stable polymorphic form of sorafenib tosylate as disclosed in Carter. One of ordinary skill in the art would be strongly motivated by Guillory to undertake those polymorphic isolation efforts. Thus, claim 1 is invalid as obvious. The recited XRD maxima are inherent properties of the obvious compound and do not render the claim non-obvious. *See Zubin*, 561 F.3d at 1360 (quoting *KSR*, 550 U.S. at 421).

Because Claim 2, which depends from claim 1 and recites additional XRD maxima of the claimed polymorph, is invalid as obvious for the same reasons as claim 1. Claim 3 depends from claim 1 and recites the IR spectrum maximum of the claimed polymorph. Claim 3 is invalid as obvious for the same reasons as claim 1. Claim 4 depends from claim 1 and recites the Raman spectrum maximum of the claimed polymorph. Claim 4 is invalid as obvious for the same reasons as claim 1 is obvious.

ii. Claim 5 is Obvious In View of Guillory and Carter

Guillory discloses the method of dissolving a compound in an inert solvent, and permitting crystals of a polymorphic form to generate. Guillory at 188. Guillory would motivate one of ordinary skill in the art to undertake these actions for the active pharmaceutical compound sorafenib tosylate, as disclosed in Carter. The thermodynamically stable form of sorafenib tosylate would form in these circumstances. *Id.* at 190-91. Combined with the reasons articulated above for claim 1, claim 5 is invalid as obvious. The recited XRD maxima are inherent properties of the obvious compound and do not render the claim non-obvious.

iii. Claim 6 is Obvious in View of Guillory and Carter

Claim 6 depends from claim 5 and recites the further step of seeding the solvent with crystals of sorafenib tosylate Form I. Guillory proposes seeding a solution of a compound with the desired polymorph. Guillory at 188. For that reason, and the reasons set forth for claim 5, claim 6 is invalid as obvious.

iv. Claim 7 is Obvious in View of Guillory and Carter

Guillory discloses the method of thermally treating crystals of a compound to obtain other polymorphic forms of the compound. Guillory at 195-97. One of ordinary skill in the art would be able to undertake the routine step of altering the parameters of temperature change to obtain the formation of polymorph form I. Guillory would motivate one of ordinary skill in the art to undertake these actions for the active pharmaceutical compound sorafenib tosylate, as disclosed in Carter. The thermodynamically stable form of sorafenib tosylate would form in these circumstances. *Id.* at 190-91. Combined with the reasons articulated above for claim 1,

claim 7 is invalid as obvious. The recited XRD maxima are inherent properties of the obvious compound and add nothing to the non-obviousness of the claim.

v. Claim 8 is Obvious in View of Guillory and Carter

The recited polymorphic form is obvious for the reasons articulated above for claim 1. Formulation of sorafenib tosylate into a composition is taught by Carter. Carter at ¶ 65. Accordingly, claim 8 is invalid as obvious.

vi. Claim 9 is Obvious in View of Guillory and Carter

Claim 9 depends from claim 8 and includes the further limitation of including inert, nontoxic, pharmaceutically suitable excipients in the composition. Carter discloses the use of such excipients. Carter at ¶ 65. Combined with the reasons articulated above for claim 8, claim 9 is invalid as obvious.

vii. Claim 10 is Obvious in View of Guillory and Carter

Claim 10 depends from claim 8 and specifies that the sorafenib tosylate present in the composition be at least 90% (by weight) sorafenib tosylate form I. As taught by Guillory, one of skill in the art would know to employ the thermodynamically stable form a compound during formulation generation. Guillory at 184. Accordingly, claim 10 is invalid as obvious.

viii. Claim 11 is Obvious in View of Guillory and Carter

Claim 11 depends from 8 and further includes a second pharmaceutical agent in the composition, where the combination of active pharmaceutical ingredients causes no unacceptable side effects. Carter teaches the combination of sorafenib tosylate with a second therapeutic agent. Carter at ¶¶ 38, 48. Further, it is axiomatic that a goal of any pharmaceutical formulation is to avoid unacceptable side effects. Thus, claim 11 is invalid as obvious.

ix. Claim 12 is Obvious in View of Guillory and Carter

Claim 12 depends from claim 8 and further includes a second pharmaceutical agent that may be a cytotoxic agent, a signal transduction inhibitor, an anti-cancer agent, or an antiemetic. Carter teaches the combination of sorafenib tosylate with a cytotoxic or cytostatic agent. Carter at ¶¶ 38, 48. Accordingly, claim 12 is invalid as obvious.

x. Claim 13 is Obvious in View of Guillory and Carter

As noted above, the recited polymorphic form is obvious for the reasons articulated above for claim 1. Formulation of sorafenib tosylate into a pharmaceutical composition with another pharmaceutical is taught by Carter. Carter at ¶¶ 38, 48, 65. The recited XRD maxima



CONFIDENTIAL
November 9, 2015
Page 105

are inherent properties of the obvious compound and do not render the claim non-obvious. Accordingly, claim 13 is invalid as obvious.

xi. Claim 14 is Obvious in View of Guillory and Carter

Claim 14 depends from claim 13 and includes the further limitation of including inert, nontoxic, pharmaceutically suitable excipients in the composition. Carter discloses the use of such excipients. Carter at ¶ 65. Thus, claim 14 is invalid as obvious.

xii. Claim 15 is Obvious in View of Guillory and Carter

Claim 15 depends from claim 13 and further includes a second pharmaceutical agent that may be a cytotoxic agent, a signal transduction inhibitor, an anti-cancer agent, or an antiemetic. Carter teaches the combination of sorafenib tosylate with a cytotoxic or cytostatic agent. Carter at ¶¶ 38, 48. Accordingly, claim 15 is invalid as obvious.

xiii. Claim 16 is Obvious in View of Guillory and Carter

The recited polymorphic form is obvious for the reasons articulated above for claim 1. The use of sorafenib tosylate to treat diseases, such as cancer, is disclosed in Carter. ¶¶ 36, 45. The recited XRD maxima are inherent properties of the obvious compound and add nothing to the non-obviousness of the claim. Thus, claim 16 is invalid as obvious.

xiv. Claim 17 is Obvious in View of Guillory and Carter

Claim 17 depends from claim 16 and specifies that the disorder is abnormal angiogenesis, hyperpermeability processes, bone marrow diseases, carcinoma and carcinogenic cell growth. Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. Carter at ¶¶ 36, 45. Combined with the reasons articulated above for claim 1, claim 17 is invalid as obvious.

xv. Claim 18 is Obvious in View of Guillory and Carter

Claim 18 depends from claim 16 and specifies that the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid, kidney, or intestine. Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. Carter at ¶¶ 36, 45. Thus, claim 18 is invalid as obvious.

xvi. Claim 19 is Obvious in View of Guillory and Carter

Claim 19 recites a method for treating a disorder, comprising administering a therapeutically effective amount of the compositions of any one of claims 8 to 15. For the same reasons articulated for claims 8 to 15, claim 19 is invalid as obvious.

xvii. Claim 20 is Obvious in View of Guillory and Carter

Claim 20 depends from claim 19 and specifies that the disorder is abnormal angiogenesis, hyperpermeability processes, bone marrow diseases, carcinoma and carcinogenic cell growth. Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. Carter at ¶¶ 36, 45. Combined with the reasons articulated above for claim 1, claim 20 is invalid as obvious.

xviii. Claim 21 is Obvious in View of Guillory and Carter

Claim 21 depends from claim 19 and specifies that the disorder is leukemia, or carcinoma of the lung, pancreas, thyroid, kidney, or intestine. Carter teaches the treatment of various cancers, including pancreatic, lung, colon, ovarian, prostate, leukemia, melanoma, hepatocellular, renal, head and neck, glioma, and mammary carcinomas. Carter at ¶¶ 36, 45. Thus, claim 21 is invalid as obvious.

xix. Claim 22 is Obvious in View of Guillory and Carter

Guillory discloses the method of dissolving a compound in an inert solvent, and permitting crystals of a polymorphic form to generate. Guillory at 188. Guillory also discusses the impact that agitation (e.g., stirring or shaking) can have on crystallization of polymorphic forms. *Id.* at 193. Guillory would have motivated one of ordinary skill in the art to undertake these actions for the active pharmaceutical compound sorafenib tosylate, as disclosed in Carter. The thermodynamically stable form of sorafenib tosylate would form in these circumstances. *Id.* at 190-91. Combined with the reasons articulated above for claim 1, claim 22 is invalid as obvious. The recited XRD maxima are inherent properties of the obvious compound and add nothing to the non-obviousness of the claim.

xx. Claim 23 is Obvious in View of Guillory and Carter

Claim 23 depends from claim 22 and includes the additional step of seeding the inert solvent with crystals of sorafenib tosylate Form I. Guillory proposes seeding a solution of a compound with the desired polymorph. Guillory at 188. Thus, claim 23 is invalid as obvious for the same reasons that claim 22 is invalid as obvious.

xxi. Claim 24 is Obvious in View of Guillory and Carter

Claim 24 depends from claim 1 and states that sorafenib tosylate Form I is made through the process of dissolving sorafenib tosylate Form II into an inert solvent and stirring or shaking the solution. Claim 24 is invalid as obvious for the same reasons that claim 22 is invalid as obvious.

xxii. Claim 25 is Obvious in View of Guillory and Carter

Claim 25 depends from claim 1 and states that sorafenib tosylate Form I is prepared by dissolving sorafenib tosylate Form II into an inert solvent, seeding with crystals of sorafenib tosylate Form I, and stirring or shaking the solution. Claim 25 is invalid as obvious for the same reasons that claim 23 is invalid as obvious.

xxiii. Claim 26 is Obvious in View of Guillory and Carter

Claim 26 depends from claim 1 and states that sorafenib tosylate Form I is prepared through thermal treatment according to the same parameters recited in claim 7. Guillory discloses the method of thermally treating crystals of a compound to obtain other polymorphic forms of the compound. Guillory at 195-97. One of ordinary skill in the art would be able to undertake the routine step of altering the parameters of temperature change to obtain the formation of polymorph form I. Guillory would motivate one of ordinary skill in the art to undertake these actions for the active pharmaceutical compound sorafenib tosylate, as disclosed in Carter. The thermodynamically stable form of sorafenib tosylate would form in these circumstances. *Id.* at 190-91. Combined with the reasons articulated above for claim 1, claim 26 is invalid as obvious.

xxiv. Claim 27 is Obvious in View of Guillory and Carter

Claim 27 depends from claim 1 and recites additional XRD maxima, the IR maximum, and Raman maximum. XRD maxima, the IR maximum and Raman maximum are inherent characteristics of a crystalline form. Claim 27 is invalid as obvious for the same reasons that claim 1 is invalid as obvious.

xxv. Claim 28 is Obvious in View of Guillory and Carter

Claim 28 recites a compound having the XRD pattern shown in Figure 2 and recites several of the XRD maxima. The XRD pattern is an inherent characteristic of a crystalline form. For the same reasons as articulated for claim 1, claim 28 is invalid as obvious.

xxvi. Claim 29 is Obvious in View of Guillory and Carter

Claim 29 depends from claim 1 and recites additional XRD maxima. XRD maxima are inherent characteristics of a crystalline form. Claim 29 is invalid as obvious for the same reasons that claim 1 is invalid as obvious.



CONFIDENTIAL
November 9, 2015
Page 108

xxvii. Claim 30 is Obvious in View of Guillory and Carter

Claim 30 depends from claim 1 and recites additional XRD maxima. XRD maxima are inherent characteristics of a crystalline form. Claim 30 is invalid as obvious for the same reasons that claim 1 is invalid as obvious.

xxviii. Claim 31 is Obvious in View of Guillory and Carter

Claim 31 depends from claim 1 and specifies that the compound of claim 1 melts under decomposition 223°C.-231°C. The physical property of melting point under decomposition is an inherent property of the obvious sorafenib tosylate Form I of claim 1. Accordingly, claim 31 is invalid as obvious for the same reasons that claim 1 is invalid as obvious.

X. Written Description

A. U.S. Patent No. 8,841,330

The '330 patent has 14 claims, each directed to a method for treating a tumor of the prostate, breast, liver, ovary, or cervix, or a method of treating liver cancer by administering sorafenib or a pharmaceutically acceptable salt thereof. For the reasons set forth below, each claim of the '330 patent is invalid under 35 U.S.C. § 112 for inadequate written description, because the specification does not describe use of sorafenib to treat tumors or cancer of the prostate, breast, liver, ovary, or cervix.

1. The '330 Patent Specification

The '330 patent specification discloses a large class of compounds that inhibit the enzyme raf kinase. The specification explains that “[t]he p21^{ras} oncogene is a major contributor to the development and progression of human solid cancers and is mutated in 30% of all human cancers.” '330 patent col.1 ll.19-21. The specification explains:

The present invention provides compounds which are inhibitors of the enzyme raf kinase. Since the enzyme is a downstream effector of p21^{ras}, the inhibitors are useful in pharmaceutical compositions for human or veterinary use where inhibition of the raf kinase pathway is indicated, e.g., in the treatment of tumors and/or cancerous cell growth mediated by raf.

Id. at col.1 ll.54-60.

The written description of the '330 patent does not mention the types of tumors or cancers recited in the claims – prostate, breast, liver, ovary, or cervix. The '330 patent instead generally states that “the compounds of the invention are useful in treating cancers, including solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).” '330 patent at col.1 l.65 – col.2 l.3.

The '330 patent does not disclose any specific data for any particular compound. *See* '330 patent at col.91 l.45 – col.93 l.38. The '330 patent discloses 103 “exemplified compounds.” '330 patent at cols.43-92. Sorafenib is disclosed as “Entry 42.” The '330 patent discloses an in vitro raf kinase assay, in vitro cellular assays, and in vivo assays for testing the disclosed compounds. The only disclosed data is that, in the in vitro raf kinase assay, “[a]ll compounds exemplified displayed IC₅₀s of between 1 nM and 10 μM.” '330 patent at col.92 ll.48-49. The '330 patent does not disclose any data at all for the in vitro cellular assays and in vivo assays, and the in vivo assays are described as assays that “can be performed.” '330 patent at col.93 ll.21-23.

2. The '330 Patent Does Not Describe Methods of Treating Cancer

The '330 patent's disclosure of treating cancer is nothing more than "a mere mention of a desired outcome." *Ariad*, 598 F.3d at 1357. The '330 patent does not describe actually treating cancer. The claims of the '330 patent, therefore, are invalid for inadequate written description.

The general statement in the '330 patent that "the compounds of the invention are useful in treating cancers, including solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma)," '330 patent at col.1 l.65 – col.2 l.3, does not provide adequate written description for claims directed to the use of the disclosed compounds to treat cancer.

Similar to the patent considered in *Ariad*, the '330 patent's specific disclosure of 103 specific compounds, with non-specific data regarding an in vitro raf kinase assay, and general statements regarding predicted usefulness in treating cancer are insufficient to describe methods of actually using those compounds to treat cancer. *See Ariad*, 598 F.3d at 1357. The written description of the '330 patent would not convey to one of ordinary skill in the art that the named inventors of the '330 patent were in possession of methods of treating cancer.

The '330 patent's disclosure of additional assays to assess the potency of the disclosed compounds, without providing any data, also provides no written description support for the claimed methods of using those compounds to treat cancer. The question is not whether the specification would have enabled one of ordinary skill in the art to test the disclosed compounds, but whether the specification discloses the claimed invention, specifically, as something the inventors actually invented. *See Novozymes A/S v. DuPont Nutrition Biosciences APS*, 723 F.3d 1336, 1350 (Fed. Cir. 2013).

The '330 patent provides nothing more than a hypothesis that the 103 "exemplified compounds" might be useful for treating cancer because those compounds have some degree of raf kinase inhibition activity. The disclosure of assays that can be used to evaluate the potency of those compounds provides nothing more than a research plan to further investigate those compounds. Such a disclosure does not provide an adequate written description for methods of treating cancer. *See Ariad*, 593 F.3d at 1353. The claims of the '330 patent, therefore, are invalid under 35 U.S.C. § 112 for inadequate written description.

3. The '330 Patent Does Not Describe Treating the Types of Cancer Recited in the Claims

Even if the '330 patent's written description could be interpreted to describe some methods of treating cancer, the written description does not describe the '330 patent's claimed methods of treating a tumor or cancer of the prostate, breast, liver, ovary, or cervix. None of those types of cancer are even mentioned in the '330 patent's written description. The only possible disclosure in the '330 patent that encompasses treating the types of cancer recited in the

claims is the general statement that “the compounds of the invention are useful in treating cancers, including solid cancers, such as, for example, carcinomas (e.g., of the lungs, pancreas, thyroid, bladder or colon), myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma).” ’330 patent at col.1 l.65 – col.2 l.3. Because the ’330 patent does not describe or even mention treatment of any of the types of tumors or cancers recited in the claims, the claims of the ’330 patent each are invalid for inadequate written description under 35 U.S.C. § 112.

4. The ’330 Patent’s Written Description Does Not Suggest The Claimed Methods

The written description of the ’330 patent not only fails to even mention the types of cancer recited in the claims, but also indicates that the disclosed compounds would not be useful for treating any and all cancers. The ’330 patent states that the disclosed raf kinase inhibitors may be useful in treating cancer, “[s]ince the enzyme [raf kinase] is a downstream effector of p21^{ras}.” The specification also explains that the p21^{ras} oncogene is mutated in only 30% of human cancers. ’330 patent at col.1 ll.19-22, 55-60. The ’330 patent’s written description, therefore, suggests that the disclosed compounds would not be useful in treating 70% of human cancers – namely, those not expressing the p21^{ras} oncogene. Nothing in the ’330 patent’s written description even suggests that the disclosed compounds could treat any and all types of cancer generally, or those recited in the claims specifically.

Additionally, the assays disclosed in the ’330 patent do not relate to the cancers recited in the claims (prostate, liver, ovary, or cervix), with the exception of breast cancer. The ’330 patent discloses in vitro cellular assays using human **colon** tumor cell lines HCT116 and DLD-1, and an in vivo assay using human **colon** adenocarcinoma cell line. ’330 patent at col.92 l.50 – col.93 l.30. The ’330 patent also references use of in vivo techniques of Brett P. Monia, et al., *Antitumor activity of a phosphorothioate antisense oligodeoxynucleotide targeted against C-raf kinase*, 2 Nature Med. 668 (1996). Monia discloses in vitro cellular assays using **lung, bladder, and colon** carcinoma cells, and in vivo mouse tumor xenograft experiments using human **lung, breast, and bladder** carcinoma cell lines. Notably, Monia states that “little is known about the potential for development of resistant tumor cell populations that lose their sensitivity toward C-raf inhibition over time” and “some tumor cells may never display sensitivity toward C-raf inhibition,” Monia 673, further supporting the conclusion that the ’330 patent’s written description would not have demonstrated to one of ordinary skill in the art that the named inventors had possession of methods of treating cancer.

5. Arguments During Prosecution Confirm the Inadequacy of the Written Description

During prosecution of the ’330 patent, the examiner found written description support for the claims based on the specification’s recitation that “the compounds of the invention are useful in treating cancers, including solid cancers” (col.1 ll.65-67) and based on several references



CONFIDENTIAL
November 9, 2015
Page 112

provided by the applicant that purportedly recite the types of solid cancers recited in the claims. Office Action 8-9 (Nov. 8, 2013).

Also during prosecution, the applicant successfully argued that an obviousness-type double patenting rejection based on parent U.S. patent no. 8,124,630 (“the ’630 patent”) did not apply. Specifically, the applicant stated:

The pending claims are directed to treating tumors of the prostate, breast, liver, ovary or cervix whereas claim [sic] 1-16 of US Patent No. 8,124,630 are directed to treating carcinoma of the lung, pancreas, thyroid, bladder or colon. The treatment methods claimed are directed to distinct cancers and are not obvious variants of the methods defined in claims 1-16 of US Patent No. 8,124,630.

Response to Office Action at 5 (Feb. 10, 2014).

Further, during prosecution of the ’330 patent, the examiner issued an obviousness-type double patenting rejection of the pending claims over the parent ’630 patent. To overcome this rejection, the applicant successfully argued that the claimed methods of treating cancer of the prostate, breast, liver, ovary, or cervix were not obvious in light of methods of treating the cancers recited in the claims of the ’630 patent (lung, pancreas, thyroid, bladder, and colon). The only carcinomas whose treatment is arguably disclosed in the written description of the ’330 patent are those recited in the claims of the ’630 patent. An argument now by the ’330 patent owner that disclosure of methods of treating cancer of the lung, pancreas, thyroid, bladder, and colon (i.e., those disclosed in the ’330 patent) describes methods of treating cancer of the prostate, breast, liver, ovary, or cervix (i.e., those claimed in the ’330 patent) would be clearly inconsistent with the argument during prosecution that methods of treating the cancers recited in the ’330 patent claims are “distinct cancers” that “are not obvious variants of” methods of treating the only carcinomas recited in the written description. Response to Office Action 5 (Feb. 10, 2014).

Because the ’330 patent’s written description does not describe the types of cancer recited in the claims, the claims are invalid under 35 U.S.C. § 112 for inadequate written description.

6. The ’330 Patent Does Not Describe Treating Cancer by Administering Sorafenib

The ’330 patent’s written description also fails to describe use of sorafenib (or any other particular compound) to treat cancer. The ’330 patent does not provide any specific data regarding the efficacy of sorafenib (or any particular compound) in *any* in vitro or in vivo assays. The only data disclosed in the ’330 patent is that, in an in vitro raf kinase assay, “[a]ll compounds exemplified displayed IC₅₀s of between 1 nM and 10 μM.” ’330 patent col.92 ll.48-



CONFIDENTIAL
November 9, 2015
Page 113

49. The '330 patent identifies 103 "exemplified compounds," but does not disclose the specific IC_{50} value for any particular compound.

Thus, the only information about the activity of sorafenib disclosed in the '330 patent is that sorafenib has an IC_{50} value somewhere between 1 nM and 10 μ M in an in vitro raf kinase inhibition assay. This range of IC_{50} values spans four orders of magnitude (10 μ M = 10,000 nM). The '330 patent provides no description of the significance of those IC_{50} values and provides no description linking those values to efficacy in treating cancer. The '330 patent provides no description to suggest that any compound having an IC_{50} value less than 10,000 nM in an in vitro raf kinase could be used to treat cancer.

One of ordinary skill in the art would not know from this disclosure which of the 103 exemplified compounds are least or most potent, and would not know if any compound having an IC_{50} value between 1 nM and 10,000 nM in an in vitro ras kinase assay could successfully treat cancer. Disclosing assays to evaluate the potency of the 103 exemplified compounds does not describe using any of those compounds to treat cancer. *See Novozymes*, 723 F.3d at 1350 (holding that adequate written description requires disclosure of the claimed invention as something the inventors invented, not mere enablement of methods to test disclosed compounds). The limited data provided in the written description of the '330 patent would not have indicated to one of ordinary skill in the art that sorafenib in particular could be used to treat cancer.

Because the written description of the '330 patent does not describe actual methods of treating tumors or cancer using sorafenib, each claim of the '330 patent is invalid under 35 U.S.C. § 112 for inadequate written description.

XI. Anticipation

A. U.S. Patent No. 8,877,933

Claims 1-4 and 27-31 of the '933 patent, which are directed to polymorphic form I of sorafenib tosylate, are inherently anticipated by the '012 publication under 35 U.S.C. § 102(b). As noted above, the '012 publication discloses the formation of sorafenib tosylate in polymorphic form II. *See* '012 publication at 41-42; *see also* '933 patent at col.2, ll.12-16; col.13, ll.35-52. Sorafenib tosylate form II, however, is a metastable polymorph, while form I is the thermodynamically stable polymorphic form of sorafenib tosylate. *Id.* at col.2, ll.12-22. Guillory proposes that "at equilibrium the product of any crystallization experiment must be the stable form, regardless of the solvent system." Guillory at 191. While "kinetic factors can for a time override thermodynamic [i.e., equilibrium] considerations," eventually the thermodynamically stable polymorphic form will be formed. *Id.* at 190-92 (discussing Ostwald's law of stages and transitions through metastable states to the most stable form). Thus, the synthesis as described in the '012 publication of sorafenib tosylate form II "naturally results in the production of" sorafenib tosylate Form I. *See Apotex*, 403 F.3d at 1344.

Stated differently, sorafenib tosylate form I "arises as a natural derivative of practicing" the prior art '012 publication. *Id.* at 1345; *see also Perricone*, 432 F.3d at 1378 ("[T]he anticipation doctrine examines the natural and inherent results in that method without regard to the full recognition of those benefits or characteristics within the art field at the time of the prior art disclosure."). Further, the '012 publication clearly enables the formation of sorafenib tosylate form I, as demonstrated by Natco's and the '933 patent's use of that process to produce sorafenib tosylate form I to the exclusion of sorafenib tosylate form II.

In light of the above, each claim of the '933 patent directed to a compound of sorafenib tosylate Form I is inherently anticipated by the '012 publication. The physical characteristics of that inherently disclosed polymorph (e.g., XRD, Raman, or IR peaks or melting point) are inherent properties of that polymorphic form. Specifically, claims 1-4 and 27-31 are directed to sorafenib tosylate Form I and its properties. As such, claims 1- 4 and 27-31 are invalid as inherently anticipated by the '012 publication.



CONFIDENTIAL
November 9, 2015
Page 115

XII. Conclusion

For the foregoing reasons, a well-informed court would find that Mylan's proposed sorafenib tosylate tablets would not infringe claims 3, 6-18, 20-23, 26, 27, 33, and 34 of the '834 patent, claims 2, 3, 5, 6, 8, 9, 11, or 12 of the '330 patent, and claims 5-7, 11-15, and 22-26 of the '933 patent, literally nor under the doctrine of equivalents. A well-informed court would further find that claims 1, 2, 4, 5, 19, 24, 25, 28-32 and 35-41 of the '834 patent, claims 1-8 of the '623 patent, claims 1-17 of the '576 patent, and claims 1-31 of the '933 patent are invalid under 35 U.S.C. § 103. A well-informed court would further find that claims 1-14 of the '330 patent would be invalid under 35 U.S.C. § 112. A well-informed court would further find that claims 1-4 and 27-31 of the '933 patent would be invalid under 35 U.S.C. § 102.



CONFIDENTIAL

November 9, 2015

Page 116

**ABBREVIATED NEW DRUG APPLICATION NO. 207012 OFFER OF CONFIDENTIAL
ACCESS PURSUANT TO 21 U.S.C. § 355(j)(5)(C)(i)(III)**

WHEREAS Mylan Pharmaceuticals Inc. (“Mylan”) has provided notice to Bayer Healthcare LLC (“Bayer”) that Mylan submitted to the U.S. Food and Drug Administration (“FDA”) an Abbreviated New Drug Application (“ANDA”) to obtain approval for Mylan to engage in the commercial manufacture, use, or sale of sorafenib tosylate tablets, 200 mg, that the ANDA has been received by the FDA and assigned ANDA No. 207012, and that the ANDA contained a Paragraph IV certification with respect to U.S. Patent Nos. 8,618,141; 7,897,623; 7,235,576; 7,351,834; 8,877,933; and 8,841,330 (collectively “the Notice Letter Patents”), which is listed in the FDA Publication, “Approved Drug Products with Therapeutic Equivalence Evaluations”;

WHEREAS this document constitutes Mylan’s Offer of Confidential Access to Bayer to that ANDA pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III) which provides:

The document providing the offer of confidential access shall contain such restrictions as to persons entitled to access, and on the use and disposition of any information accessed, as would apply had a protective order been entered for the purpose of protecting trade secrets and other confidential business information. A request for access to an application under an offer of confidential access shall be considered acceptance of the offer of confidential access with the restrictions as to persons entitled to access, and on the use and disposition of any information accessed, contained in the offer of confidential access, and those restrictions and other terms of the offer of confidential access shall be considered terms of an enforceable contract. Any person provided an offer of confidential access shall review the application for the sole and limited purpose of evaluating possible infringement of the patent that is the subject of the certification under paragraph (2)(A)(vii)(IV) and for no other purpose, and may not disclose information of no relevance to any issue of patent infringement to any person other than a person provided an offer of confidential access. Further, the application may be redacted by the applicant to remove any information of no relevance to any issue of patent infringement.

WHEREAS Mylan offers to provide Bayer confidential access to certain information from its proprietary ANDA (“ANDA Confidential Information”) subject to restrictions as to persons entitled access to, and on the use and disposition of, the ANDA Confidential Information; and

WHEREAS this document accompanies Mylan’s Notice and Detailed Statement under 21 U.S.C. § 355(j)(2)(B) with respect to the Notice Letter Patents;



CONFIDENTIAL
November 9, 2015
Page 117

NOW, THEREFORE:

1. Pursuant to 21 U.S.C. § 355(j)(5)(C)(i)(III), and subject to the restrictions contained in Section 2 below, Mylan hereby provides Bayer this Offer of Confidential Access (“Offer”) to the ANDA for the sole purpose of determining whether to bring an action with respect to the Notice Letter Patents.
2. This Offer is subject to the following restrictions as to persons entitled to access and the use and disposition of any information accessed:
 - A. **Persons Entitled to Access:** Persons entitled to access to ANDA Confidential Information (“Authorized Evaluators”) under this Offer are restricted to outside counsel engaged or employed by Bayer to represent them and the staff of such outside counsel, including paralegal, secretarial and clerical personnel who are engaged in assisting such counsel, provided that such outside counsel has been identified to Mylan in writing, and provided said outside counsel does not engage, formally or informally, in any patent prosecution for Bayer, or any FDA counseling, litigation or other work before or involving the FDA.
 - B. **Materials Accessible by Authorized Evaluators:** A copy of the ANDA Confidential Information, redacted to remove information of no relevance to any issue of patent infringement, will be provided for use by Authorized Evaluators.
 - C. **Use of the ANDA Confidential Information:**
 - i. The ANDA Confidential Information and all information contained therein or derived therefrom may be used for the sole and limited purpose of evaluating possible infringement of the Notice Letter Patents and for no other purpose. By way of non-limiting example only, the ANDA Confidential Information shall not be used to prepare or prosecute any future or pending patent application by Bayer, or in connection with any filing to, or communication with, FDA relating to the ANDA.
 - ii. Authorized Evaluators shall not disclose any ANDA Confidential Information contained in or derived from the ANDA or any notes, analyses, studies or other documents to the extent that they reflect any ANDA Confidential Information, to any person other than Authorized Evaluators.
 - iii. Notwithstanding the provisions of subsections 2(C)(i) and 2(C)(ii) above, Authorized Evaluators shall be permitted to advise Bayer whether or not to bring suit alleging infringement of the Notice Letter Patents; provided, however, that the ANDA Confidential Information is not thereby disclosed.



CONFIDENTIAL

November 9, 2015

Page 118

D. Disposition of the Information in the ANDA:

- i. Bayer agrees that if no suit is filed against Mylan alleging infringement of the Notice Letter Patents within 45 days of receipt of this Offer, Bayer shall cause Authorized Evaluators, within 30 days after the expiration of the 45-day period, to destroy or return to Mylan the ANDA Confidential Information and all notes, analyses, studies or other documents to the extent that they contain ANDA Confidential Information, and Bayer shall promptly notify Mylan that this has been done.
- ii. Bayer agrees that if a suit is filed against Mylan alleging infringement of the Notice Letter Patents within the 45-day period:
 - a) While the litigation is pending, the ANDA Confidential Information and all notes, analyses, studies or other documents to the extent that they contain ANDA Confidential Information, shall be treated as information under the highest level of confidentiality under any protective order entered in the action brought against Mylan. Until such a protective order is entered, subsection 2(C)(ii) above continues to apply.
 - b) No ANDA Confidential Information shall be included in any publicly-available complaint or other publicly available pleading.
 - c) Bayer shall cause Authorized Evaluators to destroy or return to Mylan the ANDA Confidential Information provided and all notes, analyses, studies or other documents prepared to the extent that they contain ANDA Confidential Information, within thirty (30) days after the final determination of the action brought against Mylan.
- iii. Notwithstanding the provisions of subsections 2(D)(i) and 2(D)(ii) above, each outside counsel authorized to have access pursuant to subsection 2(A) shall be permitted to retain one copy of the portions of ANDA Confidential Information provided and each note, analysis, study or other document to the extent that they contain ANDA Confidential Information.

E. Accidental Disclosure: Should ANDA Confidential Information be disclosed, inadvertently or otherwise, Bayer shall, at its earliest opportunity, by and through Authorized Evaluators, contact Mylan and identify:

- i. what has been disclosed;
- ii. the individuals to whom such information has been disclosed; and



CONFIDENTIAL
November 9, 2015
Page 119

- iii. steps taken by Bayer and Authorized Evaluators to ensure the ANDA Confidential Information is not further disseminated.
3. Bayer acknowledges that violation of any provision of this Offer will cause irreparable injury to Mylan and that an adequate legal remedy does not exist. Mylan, therefore, shall have the right, in addition to any other remedies available at law or in equity, to obtain from a court of competent jurisdiction an injunction to prohibit Bayer from violating the terms of this Offer. Bayer agrees that in such an action Mylan is entitled to recover any and all damages, costs and expenses, including, but not limited to, all reasonable attorneys' fees, professional fees and court costs.
4. Should any provision set forth in this Offer be found by a court of competent jurisdiction to be illegal, unconstitutional or unenforceable, the remaining provisions shall continue in full force and effect.
5. Nothing contained herein shall be construed as a grant of any license or other right to use the ANDA Confidential Information except for the purpose expressly stated herein.
6. When accepted by Bayer, this document shall constitute the entire agreement of the parties with respect to the subject matter herein and may not be amended or modified except in writing executed by all of the parties.
7. This Agreement shall be construed in accordance with the laws of the State of West Virginia, without regard to its conflict of laws provisions.
8. Nothing in this Offer shall be construed as an admission by Mylan regarding the validity, enforceability, and/or infringement of any U.S. patent. Further, nothing herein shall be construed as an agreement or admission by Mylan with respect to the competency, relevance, or materiality of any such ANDA Confidential Information, document, or thing. The fact that Mylan provides ANDA Confidential Information upon request by Bayer shall not be construed as an admission by Mylan that such ANDA Confidential Information is relevant to the disposition of any issue relating to any alleged infringement of the Notice Letter Patents, or to the validity or enforceability of the Notice Letter Patents.
9. Bayer may request access to the ANDA Confidential Information by executing a copy of this Offer where indicated and returning the executed copy to: Douglas Carsten, Wilson Sonsini Goodrich & Rosati, 12235 El Camino Real, Suite 200, San Diego, California 92130. Thereupon, the terms contained in this document shall be considered an enforceable contract between Mylan and Bayer.



CONFIDENTIAL
November 9, 2015
Page 120

Mylan Inc. and Mylan Pharmaceuticals Inc.
By its Counsel:

Bayer Healthcare LLC
By its authorized agent:



Wilson Sonsini Goodrich & Rosati
Douglas Carsten

Dated: November 9, 2015

Signature: _____

Name (Print): _____

Title: _____

Date: _____

EXHIBIT 11

REDACTED
IN ITS
ENTIRETY

EXHIBIT 12

**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

BAYER HEALTHCARE LLC, BAYER
HEALTHCARE PHARMACEUTICALS INC.,
and ONYX PHARMACEUTICALS, INC.,

Plaintiffs,

v.

MYLAN PHARMACEUTICALS INC. and
MYLAN INC.,

Defendants.

Civil Action No. 1:15-cv-114

EXPERT REPORT OF DR. RON BIHOVSKY

I. BACKGROUND

a. Professional Background and Qualifications

1. I am a chemistry expert with a particular expertise in organic synthesis and medicinal chemistry, and have more than 35 years of academic and industrial chemistry experience in these areas. I have served as an expert in numerous biotechnology and pharmaceutical cases, including many which required laboratory investigations. The following is a brief summary of my background, experience, publications, and achievements, which are more fully set out in my *curriculum vitae*, a copy of which is attached as Exhibit A.

2. I am an organic and medicinal chemist by training. I received a Bachelor of Science degree, magna cum laude, with honors in chemistry from Stony Brook University. In 1977, I earned a Ph.D. in organic chemistry from the University of California, Berkeley, and subsequently was a National Institute of Health postdoctoral fellow at the University of Wisconsin, Madison from 1978 until 1980. My Ph.D. and postdoctoral research involved the synthesis and structure

elucidation of organic compounds possessing biological activity including saxitoxin, anatoxin-a, G-acid, and leukotriene. Details are noted in my *curriculum vitae*.

3. I began my independent career as a professor of organic chemistry at Stony Brook University in 1980, where I performed organic chemistry research, synthesized natural products, supervised graduate students and postdoctoral fellows, and taught classes in organic chemistry including graduate-level organic synthesis. My research continued to focus on the synthesis and structure elucidation of biologically-active compounds including biotin, oudenone, civet acid, papulacandin, C-glycoside antibiotics, pseudomonic acid, lignans, crown gall metabolites and tetrahydroisoquinolones. Details are noted in my *curriculum vitae*.

4. From 1987 until 2001, I worked in the pharmaceutical industry as a medicinal chemist in roles of increasing responsibility at Berlex Laboratories and Cephalon Inc. where I synthesized numerous classes of molecules ranging from heterocycles to peptide mimetics as potential pharmaceuticals, supervised project teams of medicinal chemists, and as project leader developed research strategies in collaboration with my colleagues in biochemistry and pharmacology. I identified a peptide mimetic amide replacement which was incorporated into angiotensin II analogs, developed epoxysuccinate inhibitors of cysteine proteases, potent endothelin- converting enzyme inhibitors, calpain inhibitors, and PARP inhibitors. These compounds were tested in animal models of disease including hypertension, cerebral ischemia and cancer.

5. In 2001, I founded Key Synthesis LLC, an organic chemistry laboratory, located in Wynnewood, Pennsylvania, where I am currently the president. At Key Synthesis, I perform custom synthesis of biologically-active organic compounds for the pharmaceutical, biotechnology, and agrochemical industries. Key Synthesis is fully equipped to conduct custom organic synthesis, contract medicinal chemistry research, consulting and process research for these industries.

6. I have presented my research at national and international scientific meetings, including American Chemical Society national meetings and Gordon Conferences. I have also

published my research in approximately 50 peer reviewed journal articles, in publications such as Journal of Organic Chemistry, Journal of the American Chemical Society, and Journal of Medicinal Chemistry. I have been granted 15 US patents and numerous foreign patents, generally directed to novel compounds with pharmaceutical activity.

7. From 2001 to 2003, I was also an adjunct professor at Villanova University where I taught courses including organic chemistry and graduate-level medicinal chemistry.

8. I served as chairman of the Chemical Consultants Network, a topical group of the American Chemical Society, from 2009 to 2012, and have served on its steering committee from 2007 to present.

9. Based on my education, practical training, teaching, research, publications, patents, consulting, and industrial experience, I consider myself an expert in the areas of organic and medicinal chemistry, with a special emphasis on enzyme inhibitors.

II. COMPENSATION AND PRIOR TESTIMONY

10. I have served as an expert on about 40 patent litigation cases, most of which were settled. I have testified at two trials. During the past four years, I was deposed in the following cases:

- a. *Shire v. Amneal et al.*, C.A. No. 2:11-cv-03781, D.N.J.
- b. *Otsuka v. Alkem Laboratories*, C.A. No. 1:15-cv-8305-JBS-KMW, D.N.J.

11. I have reviewed the Opening Expert Report of Dr. Michael Grossbard, and incorporate his report herein by reference, including his discussion relating to angiogenesis and mechanism of action.

12. I am being compensated at my customary rate of \$300/hour for expert consulting on this matter and \$350/hour plus expenses for laboratory work or testimony. My compensation has not influenced my view on any of these matters and does not depend in any way on the outcome in this case.

III. ASSERTED CLAIMS AND SUMMARY OF OPINIONS

13. If called as an expert witness in this matter, I anticipate that my testimony may concern the matters addressed below. Additionally, since this report addresses only validity issues, I anticipate that I may comment on materials relating to these matters that later become available, such as expert reports or deposition testimony. I reserve the right to supplement or amend this report, including by rebutting or agreeing with opinions expressed in reports by other experts. In connection with my testimony, I may present visual aids and demonstrative exhibits that illustrate the analysis discussed in this report.

14. I understand that Bayer Healthcare LLC, Bayer Healthcare Pharmaceuticals Inc., and Onyx Pharmaceuticals, Inc. (“plaintiffs”) are asserting six patents against Mylan in this litigation: U.S. Patent No. 8,618,141 (“the ’141 patent”), U.S. Patent No. 7,897,623 (“the ’623 patent”), U.S. Patent No. 7,235,576 (“the ’576 patent”), U.S. Patent No. 7,351,834 (“the ’834 patent”), U.S. Patent No. 8,877,933 (“the ’933 patent”), and U.S. Patent No. 8,841,330 (“the ’330 patent”). For purposes of my report, I have focused on the ’576, ’623, and ’834 patents.

15. I understand that the plaintiffs are asserting the following claims against Mylan: claims 14-16 of the ’576 patent, claims 1-6 of the ’623 patent, and claims 39-41 of the ’834 patent.

16. In my opinion, the asserted claims of the ’576 patent, the ’623 patent, and the ’834 patent disclose compounds and salts thereof that would have been obvious to a person of ordinary skill in the art.

17. Specifically, the asserted claims of the ’834, ’623, and ’576 patents would have been obvious to a person of ordinary skill at the time of the invention over:

- a. PCT International Publication No. WO 97/04765 to Winkler, et al., in view of U.S. Patent No. 4,863,924 to Haga, et al., PCT International Publication No. WO 97/40028 to Armistead, et al., U.S. Patent Published Application 2008/0269265 to Miller, et al., U.S. Patent No. 7,517,880 to Miller, et al., PCT International Publication No. WO 99/32436 to Miller, et al., or PCT

International Publication No. WO 99/32106 to Dumas, et al. (collectively “Lead Structures”), in light of the knowledge and interests within the industry at the time;

And in further view of the guidelines set forth for balancing potency and bioavailability, as taught by:

- b. Lipinski, et al., “Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings,” *Adv. Drug Delivery Reviews*, 23:3-25 (1997), Curatolo, W., “Physical chemical properties of oral drug candidates in the 'discovery and exploratory development settings,” *PSTT*, 1(9):387-393 (Dec. 1998), and “Data From SRC PhysProp Database.”

18. It is my opinion that the availability of rapid screening and automation techniques, including high throughput screening and combinatorial chemistry would further motivate a person of ordinary skill in the art to evaluate large numbers of potential drug compounds. Sorafenib and sorafenib tosylate are obvious variants from the Lead Structures, and would emerge from these routine screens and tests as unsurprising drug candidates.

19. It is my opinion that a person of ordinary skill in the art would cast a wide net to find potential drug targets, especially given the availability and efficiency of screening techniques and tools.

20. It is my opinion that a person of ordinary skill, aware of the interest surrounding the diaryl urea core scaffold in compounds that may play a role in cell proliferation, would be motivated to consider such compounds as starting points for drug discovery.

21. It is my opinion that a person of ordinary skill in the art would find it obvious to try and would be motivated to incorporate a structure such as the N-methyl picolinamide group into the Lead Structures. The effectiveness of a drug candidate depends upon several factors, including potency and bioavailability. Enhancing bioavailability requires balancing solubility and cellular

permeability. Nicotinamide (also known as 3-pyridinecarboxamide) and picolinamide (also known as 2-pyridinecarboxamide) were known for their solubility in water. Considerations of permeability and potency would motivate a person of ordinary skill in the art to incorporate structures such as a N-methylpicolinamide, an obvious derivative of picolinamide, into the Lead Structures.

IV. TUTORIAL

22. For purposes of preparing for my consultation and potential witness services, I have reviewed relevant literature and materials, which are listed in Exhibit B.

23. I provide a tutorial below, which reflects what was known by a person of ordinary skill in the art (“POSA”) at the relevant time.

a. Drug Discovery

24. Drug discovery is the process by which one analyzes a potentially large number of compounds to find candidates that would have clinical potential. Drug discovery can be loosely categorized into five stages. These stages generally include 1) literature research, 2) screening to obtain hit compounds, 3) identification of lead compounds, 4) development of lead compounds, and 5) optimization of lead compounds.

b. Assay and Screening Techniques

25. One of the first steps in drug discovery is exploring what is already known about the disease one is attempting to treat. Part of this research involves understanding what others have published in terms of potential drug candidates and promising drug scaffolds or core structures. Whether certain compounds reached clinical trial stage is not a determinative factor for the decision to pursue research into potential drug candidates, drug scaffolds, or core structures.

26. Several well-known companies offered large numbers of ready-made compounds for purchase in the late 1990s, including companies such as Maybridge, Aurora, ChemBridge, and Enamine. These compound libraries provided a POSA an opportunity to screen for “hits,” which is understood to mean compounds with activity in a biochemical assay such as an enzyme assay and/or cell assay.

27. The techniques used for evaluating potential hits were well known in the art as of the late 1990s. Specifically, high throughput screening (“HTS”) is a technique that was widely used by the industry. HTS utilized automation such as robotics, liquid-handling systems, and computerized control to rapidly measure the pharmacological properties of large numbers of compounds. Through automation of the system, there has been a momentous increase in the number of compounds that can be analyzed on a small scale within a short period of time and with lesser cost. Further, the potential for human error in laboratory technique (for example, in the exactness of pipetting) is eliminated, therefore yielding more robust and reliable results. *See* McDonald, et al., “A Scintillation Proximity Assay for the Raf/MEK/ERK Kinase Cascade: High-Throughput Screening and Identification of Selective Enzyme Inhibitors,” *Analytical Biochemistry*, 268:318-329 (1999) (“McDonald”); Lipinski, et al., “Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings,” *Adv. Drug Delivery Reviews*, 23:3-25 (1997) (“Lipinski”), at 23; *see also* Curatolo, W., “Physical chemical properties of oral drug candidates in the discovery and exploratory development settings,” *PSTT*, 1(9):387-393 (Dec. 1998) (“Curatolo”).

28. Enzyme screens were also available since at least the 1980s to evaluate the potency of potential hits. Enzyme screens provide data that show the level of activity of the synthesized compounds. A common measurement of activity is IC_{50} data. A compound’s IC_{50} value is defined as the concentration of the compound necessary to inhibit 50% of an enzyme’s activity. Therefore, the smaller the IC_{50} value, the more potent the compound.

29. A typical standard used to maintain a manageable number of hit compounds for further study is an IC_{50} value of 1 μ M or less, and can be adjusted accordingly to the number of hits obtained. A “hit series” is obtained once compounds are identified that have the requisite IC_{50} values. A hit series can consist of an identified Markush group.

30. Combinatorial chemistry was another well-known technique by the late 1990s. Combinatorial chemistry encompasses various technologies for the rapid synthesis of large

numbers of compounds, often referred to as libraries of compounds, to facilitate the identification of new active compounds for testing by HTS techniques. Wilhelm at 836. Khire, et al., “Omega-carboxypyridyl substituted ureas as Raf kinase inhibitors: SAR of the amide substituent,” *Bioorganic & Medicinal Chemistry Letters*, 14:783-786 (2004) (“Khire”).

31. Kinases are a family of enzymes which transfer phosphates from molecules such as ATP to substrates including peptides and proteins, transmitting signals and regulating cell processes. Specifically, a POSA was able to use the screening and analytical methods known at the time to measure the activity of potential lead molecules for a variety of kinases. *See* Zimmermann, et al., “Potent and Selective Inhibitors of the ABL-Kinase: Phenylamino-Pyridimidine (PAP) Derivatives,” *Bioorganic & Medicinal Chem. Letters*, 7(2):187-192 (1997) (“Zimmermann”); de Wit, et al., “Large Scale Screening Assay for the Phosphorylation of Mitogen-Activated Protein Kinase in Cells,” *J. Biomolecular Screening*, 3(4):277-284 (1998) (“de Wit”), at 277 (describing the use of “large-scale screening of the effectivity of biological or chemical compounds that modulate the cellular response to physiologic stimuli or stress through phosphorylation and activation of MAP kinase,” within the family of MAP kinases including p38 and Raf-mediated ERKs); Ramdas, L. & R.J.A. Budde, “An Automated Liquid-Phase Assay for Quantitation of Protein Tyrosine Kinase Activity,” *Analytical Biochem.*, 254:291-293 (1997) (“Ramdas”) (emphasizing that “[i]t is becoming increasingly important now with the advent of combinatorial chemical libraries to develop assays to screen a large number of chemical compounds against multiple targets,” and describing liquid-phase assays for automation as “rapid” and “simple”). *See also* Wilhelm, et al., “Discovery and development of sorafenib: a multikinase inhibitor for treating cancer,” *Nature Reviews Drug Discovery*, 5:835–844, (2006) (“Wilhelm”). In the Abstract, the authors state that the introduction and refinement of rapid HTS technologies over the past decade, had greatly facilitated this targeted discovery and development process. *Id.* at abstract.

32. Specifically, by around 1989, HTS and combinatorial chemistry (see below) rapidly grew as a major paradigm for discovery of new chemicals. *Id.* at 836. The authors recognized that

in 1994, when the project team was formed, “the reagents and assays were available to identify a Raf kinase inhibitor. A scintillation proximity assay for the ... (HTS) and identification of selective Raf/MEK/ERK enzyme inhibitors had already been developed by McDonald *et al.* at Glaxo-Wellcome Inc.,” showing that this approach was feasible and did not require undue experimentation. *Id.*

33. Tumor cell lines that contained oncogenic k-ras and/or b-raf mutations demonstrated upregulated signaling through the Raf/MEK/ERK pathway. Such tumor lines would be vital for performing the necessary in vitro and human tumor xenograft studies required to identify and select candidate raf kinase inhibitors for further evaluation in Phase I clinical trials. In fact, Wilhelm states that “the essential tools were available to proceed with the discovery and development of a novel targeted Raf1 kinase inhibitor for the treatment of cancer.” *Id.*

34. Indeed, as admitted by the named inventors, the tools and techniques required to identify a Raf kinase inhibitor were also known. Wilhelm, at 836 (“When the project team was formed in 1994, the reagents and assays were available to identify a Raf kinase inhibitor.”). The well-known HTS method was used to determine that a particular 3-thienyl urea was “a promising lead compound” by comparing IC₅₀ inhibitory data. *Id.* at 836, Figure 1 (Raf1 inhibitor 1). Gathering and analyzing IC₅₀ data was well within the routine practice of drug discovery. McDonald at 327; WO 96/40673 (“Tang”) at 36.

35. Combinatorial chemistry can facilitate the identification of one or more lead compounds by generating a large number of compounds which can be screened against recombinant human raf-1 kinase. Combinatorial chemistry can also be utilized to optimize initial lead compounds to yield potent, orally active raf-1 kinase inhibitors. Khire at 783.

36. Combinatorial chemistry, enzyme assays, and HTS techniques allowed the medicinal chemist, often in a relatively short time, to convert novel leads to compounds with in vitro potency suitable for a potential drug candidate. This stage of the discovery process was considered by many to be highly predictable. *See, e.g.,* Lipinski at 23 (referring to combinatorial

chemistry and HTS as “[e]stablished methodology” that “produce leads with an efficiency that compares favorably with ‘rational’ drug design, and perhaps more importantly, because these techniques expand the breadth of therapeutic opportunities and hence the leads for drug discovery.”).

c. Development of Lead Compounds

37. Once initial hits are obtained, a POSA would thereafter optimize the potency of one or more of the initial hits. For example, a POSA would modify a given structure to optimize potency in an enzyme assay and/or cell assay. A POSA may consider various parameters for the desired variations, including size (i.e. Van der Waals radii), shape, electron density, lipophilicity, hydrophilicity, hydrogen bonding potential, polar surface area, and molecular weight. The most promising candidates of the hit series constitute what would be considered a lead series.

38. A lead series may contain multiple lead compounds – compounds that have potential in vitro efficacy. It is well known in the industry that in the search for potential drug candidates, one would frequently have more than one lead compound. It is likely that one would study multiple lead compounds, often simultaneously, based on a set of selection criteria that may include the compounds’ selectivity, permeability, solubility, microsomal stability, and ease of synthesis. It is also not atypical to develop “generations” of lead compounds, where each generation of lead compounds builds upon the knowledge gained from the previous generation. It would also not be unusual to have lead compounds that are essentially hybrids of other compounds, especially if the compounds shared a common core structure of interest. In fact, one can learn from the structures of compounds from different lead series and overlay them to obtain promising hybrid structures that capitalize on the learnings from the different lead series.

d. Optimization of the Lead Compound

39. Once lead compounds are identified, a POSA would optimize the structures of the lead compounds. One of the first steps of this process is analyzing the structure activity relationship

of the compounds, which consists of studying the impact that changes to a compound have to its potency against a specific target in a specific assay.

40. The effectiveness of an oral drug compound is correlated to potency and bioavailability. Bioavailability, in turn, depends upon a balance between solubility and cellular permeability. In other words, for a compound to be effective, it must dissolve sufficiently within the bloodstream, and also be sufficiently permeable to interact effectively with the cell.

41. Since at least 1996, it has been known that nicotinamide (also known as 3-pyridinecarboxamide) and picolinamide (also known as 2-pyridinecarboxamide) have high solubility in water, 5×10^5 mg/L and 1.8×10^5 mg/L, respectively, as indicated in the data from “Data From SRC PhysProp Database” (“SRC PhysProp Database”). In my opinion, a POSA seeking to enhance the solubility of an anti-cancer drug would incorporate structures that enhance solubility, such as the picolinamide into lead compounds. At the same time, a POSA would be motivated to also consider factors that would enhance permeability, potency, and the compound’s binding potential to an enzyme receptor pocket, as disclosed by Lipinski. Lipinski at 15. The POSA would therefore consider N-methylpicolinamide, an obvious derivative of picolinamide, as a potential structure to incorporate into compounds. *See* SRC PhysProp Database.

42. The lead compound optimization process has been greatly enhanced by automation techniques. For example, computers can perform similarity searches of the most active compounds and find structural matches within this subset of active compounds. A POSA can further customize this automated analysis by providing additional parameters, such as molecular weight, solubility, potency, steric considerations, and hydrophilicity to generate potential structures that can be made that fit within these criteria.

43. Lipinski conducted experimental and computational studies of the World Drug Index database to estimate solubility and permeability in the discovery and development phase of drug-like lead compounds, finding that “the rule of 5” can be used at the discovery stage to predict absorption or permeation of lead compounds. Specifically, Lipinski’s “rule of five” predicts that

poor adsorption or permeation of a drug-like compound is more likely when there are more than 5 H-bond donors, 10 H-bond acceptors, a molecular weight of greater than 500, and the calculated log P (ClogP) of greater than 5. Lipinski at Abstract. Further, in describing the selection a lead compound, Lipinski stated that “[o]ne of the most reliable methods in medicinal chemistry to improve in vitro activity is to incorporate properly positioned lipophilic groups. For example, addition of a single methyl group that can occupy a receptor ‘pocket’ improves binding by about 0.7 kcal/mole.” *Id.* at 5

44. Oral efficacy is a function of potency and oral bioavailability. Curatolo at 388. Oral bioavailability is the fraction of the drug absorbed through oral administration compared with intravenous administration. Oral bioavailability is a function of the drug that is absorbed by the intestine into the portal blood when administered orally. The fraction of drug absorbed into the portal blood is a function of the solubility of the drug relative to dose, and the intrinsic permeability of the intestinal wall to the drug, reflected in a permeability measurement or an absorption rate constant. Curatolo at 388. Selecting a lead compound likely to have physico-chemical properties and consistent with good absorption must be balanced with potency. Curatolo teaches that an ideal lead compound exhibits a balance between target binding activity and permeability. Curatolo at 387-392.

45. Accordingly, once efficacious lead compounds are identified, applying filters to obtain a compound of increased permeability and solubility would enhance the chances of a lead compound to progress to preclinical studies. These routine considerations would guide a POSA to a subset of compounds that meet these requirements. With the availability of rapid screening and automation techniques, the sorafenib structure would present itself as an obvious drug candidate and as an obvious variant from the lead compounds known in the art. Lipinski at 23.

e. Scope of Cancer Targets

46. As of the late 1990s, much was still being learned about the specific pathways relating to cancer. While it was readily understood that solid tumors were linked to angiogenesis

and cell proliferation, there was not substantial information on the roles of specific inhibitors, receptors, and pathways for each kind or instance of tumor formation.

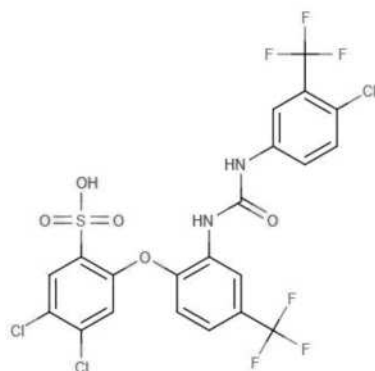
47. Therefore, the scope of potential compounds of interest was broad. POSA would consider many different potential targets for developing potential cancer drug compounds. A POSA would consider compounds known to play a role in cell proliferation and angiogenesis. This would include, for example, a wide variety of enzyme inhibitors. Therefore, a POSA seeking drug candidates for the treatment of cancer would focus on compounds, drug scaffolds, or core structures that have been reported as having potential anti-angiogenic and/or anti-proliferative effects.¹

V. KNOWLEDGE OF THE DIARYL UREA CORE SCAFFOLD

a. General Anti-Cell Proliferation and Anti-Angiogenesis Properties

48. The diaryl urea core is disclosed in publicly available literature as part of structures that were hypothesized to play a role in cell proliferation and cancer in general. *See, e.g.*, PCT International Publication No. WO 97/04765 to Winkler, et al. (“Winkler”). Winkler is directed to the use of inhibitors of CoA-independent transacylase (CoA-IT) to treat cell proliferation and cancer. CoA-IT is an enzyme responsible for transferring arachidonate between phospholipids of inflammatory cells. *Id.* at 2:22-24. Winkler discloses that three inhibitors of CoA-IT, ET-18-O-CH₃, diethyl 7-(3,4,5-triphenyl-2-oxo-2,3-dihydro-imidazol-1-yl)heptane-phosphonate, and 2-[2-[3-(4-chloro-3-(trifluoromethylphenyl)ureido)-4-trifluoromethyl phenoxy]-4,5-dichlorobenzene sulfonic acid (Compound I^a) induce apoptosis (programmed cell death) of HL-60 human leukemia cells. *Id.* at 7:4-10. 2-[2-[3-(4-chloro-3-(trifluoromethylphenyl)ureido)-4-trifluoromethyl phenoxy]-4,5-dichlorobenzene sulfonic acid (Compound I^a), is a urea compound which has the following structural formula:

¹ I have reviewed the Opening Expert Report of Dr. Michael Grossbard, and incorporate his report herein by reference, including his discussion relating to angiogenesis and mechanism of action.



Winkler at 6, 11, Table 1, Compound I^a.

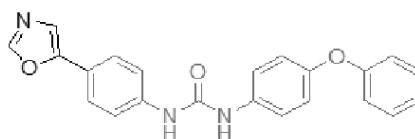
49. Compound I^a inhibits CoA-IT with an IC₅₀ of 6 μ M against human leukemic cell line HL-60. *Id.* at 11, Table 1, Compound I^a. Compound II^b is a structurally related urea compound. However, it does not inhibit CoA-IT or induce apoptosis of HL-60 cancerous cells. *Id.* at 11, Table 1, Compound II^b. It is noteworthy that Compound I^a has the same urea structure connected to a 4-chloro-3-(trifluoromethyl)phenyl moiety at one end and two aromatic groups connected by oxygen at the other end of NH-CO-NH urea moiety as found in sorafenib. Winkler further teaches pharmaceutically acceptable salts of the disclosed compounds. *Id.* at 3. A sodium salt of Compound I^a is described in Example 2. *Id.* at 19-20.

50. Compound I was disclosed in several additional references. *See, e.g.,* Chilton, et al., “Inhibitors of CoA-Independent Transacylase Block the Movement of Arachidonate into 1-Ether-Linked Phospholipids of Human Neutrophils,” *Biochemistry*, 34:5403-5410 (1995) (“Chilton”); Winkler, et al., “Effects of CoA-Independent Transacylase Inhibitors on the Production of Lipid Inflammatory Mediators,” *JPET*, 274(3):1338-1347 (1995) (“Winkler 1995”); Winkler, et al., “Inhibitors of Coenzyme A-Independent Transacylase Induce Apoptosis in Human HL-60 Cells,” *JPET*, 279(2):956-966 (1996) (“Winkler 1996”).

51. Compound I was tested in a variety of in vitro and cell line assays to understand the biological activity, potency, and selectivity of Compound I. The Winkler References show that Winkler Compound I had significant biological activity and selectivity, including inducing

apoptosis and inhibiting cell growth of human promyelocytic leukemia (HL-60) cells. *See, e.g.*, Winkler 1995 at 1340-1346; Winkler 1996 at 958-964; Chilton at 5406-5409.

52. A related group of compounds which incorporate the diaryl urea core structure was claimed to have inhibitory effects against various forms of cancer. *See, e.g.*, PCT International Publication No. WO 97/40028 to Armistead, et al. (“Armistead”). Armistead teaches a class of compounds that are inosine monophosphate dehydrogenase inhibitors (IMPDH) which, in a preferred embodiment, may also be used to inhibit tumors and cancer in a mammal, for example lymphoma, leukemia and other forms of cancer. *Id.* at 43:21-26, 88:23-32). Among these compounds, Compound 21 is closest in structure to Winkler Compound I^a:



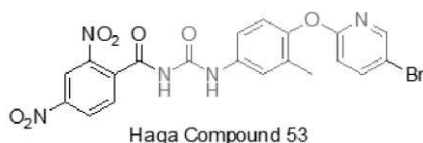
Armistead Compound 21

Id. at 22, Table IB.

53. Armistead also teaches that the compounds may be modified by appending appropriate functionalities to enhance biological properties including increased solubility. *Id.* at 32:27–33:3. Armistead further teaches pharmaceutically acceptable salts of the disclosed compounds, including those derived from pharmaceutically acceptable inorganic and organic acids, such as tosylate. *Id.* at 29:1-28.

54. Other examples of the diaryl urea core are disclosed in U.S. Patent No. 4,863,924 to Haga, et al. (“Haga”). Haga discloses N-benzoyl urea compounds useful for the treatment of tumors or cancer and “which exhibit excellent antitumor activities ... without bringing about side effects.” Haga at 1:59-65. Haga teaches that Compound 53 increases life span (ILS) by 106% to 184% when administered intraperitoneally or orally to mice carrying p-388 leukemia cells. *Id.* at Table 5, Compound 53 and Table 6-3, Compound 53.

55. Compound 53 has the following structure:

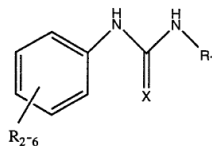


56. Haga's Compound 53 is a structure similar to Winkler's Compound I^a. *Id.* at Table 4 and 3:8-9. Haga also teaches that the disclosed urea compounds have poor solubility in both water and organic solvents. *Id.* at 26:3-4.

b. Kinase Inhibition Activity

57. The diaryl urea core structure was already known to be a potential kinase inhibitor as early as 1996. Dumas, J., "Protein kinase inhibitors from the urea class," *Current Opinion in Drug Discovery & Development*, 5(5):718-727 (2002) ("Dumas I"); *see also* Dumas, et al., "Recent developments in the discovery of protein kinase inhibitors from the urea class," *Current Opinion in Drug Discovery & Development*, 7(5):600-616, (2004) ("Dumas II"), at 600 ("[i]nhibitors from the urea class were first reported in 1996 and have emerged as an important compound class for medicinal chemists due to their unique binding mode and kinase inhibition profile."). In particular, the inventors state that "[u]rea-based kinase inhibitors were first described by Sugen . . . in 1996," citing WO 96/40673 ("Tang"). Dumas I at 718.

58. Tang is directed to compounds having the formula:



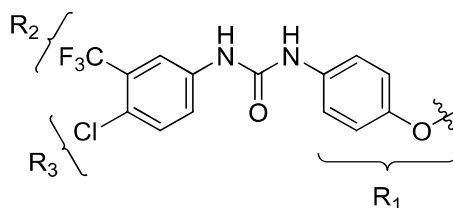
and pharmaceutically acceptable salts thereof, wherein X can be O or S, where R₁ is selected from a group consisting of optionally substituted **aryl**, alkylaryl, and heteroaryl, and where R₂₋₆ are independently selected from the group consisting of hydroxy, H, alkyl, alkoxy, CN, nitro, **halo**, **trihalomethyl**, amide, carboxamide, sulfonyl, and sulfoxamide. *Id.* at 3:14-24, emphasis added.

59. Tang further describes such compounds as potentially useful for treating a large and diverse array of disorders related to cell proliferation:

[I]nhibiting cell proliferation [or] differentiation and related disorders. Examples of such disorders include cancers, blood vessel proliferative disorders, psoriasis, hyperimmune response and fibrotic disorders. Examples of other disorders include the HER2 disorders, EGF disorders, IGFR disorders, PDGFR disorders, met disorders, SVC disorders, and KDR/FLK-1 disorders described herein. It is to be understood that compounds which are effective for diseases related to one RTK will also be likely be effective for diseases related to other RTK's, especially those from the same family.

Id. at 4:4-12. *See also id.* at 6-17.

60. Claim 2 of Tang claims the compound wherein X is O. *Id.* at 87:13. Claim 6 of Tang claims the compound wherein R₁ is an aryl substituent. *Id.* at 87:19. Tang provides further modifications of the diaryl urea core. For example, Tang specifies that a preferred embodiment of the invention includes aryl substituents that contain trihalomethyl substituents. Tang at 5. Trihalomethyl substituents would include a CF₃ substituent attached to the aromatic group. Hence, Tang discloses the below structure as a preferred embodiment:



Id.

61. Tang discloses that these diaryl ureas inhibit kinase activity. Furthermore, tyrosine kinase inhibitors are often active against multiple kinases, including raf kinase. *See, e.g.*, WO 99/10325A1 (“the ’325 application”) at Abstract, 137:17-24. Specifically, claim 34 of the ’325 application discloses the use of compounds for treating diseases associated with over 25 different kinases. *Id.* at 137:17-24. A POSA would thus have considered a variety of references in search of an inhibitor of the RAF/RAS/MEK pathway.

62. The diaryl urea core was also part of compounds postulated as potential inhibitors of the protein kinase p38. WO 99/00357, published on January 7, 1999, is a PCT application entitled “Inhibitors of p38” (“the ’357 publication”). p38 inhibitors inhibit protein kinases involved in cell proliferation, cell death and response to extracellular stimuli. The invention provides pharmaceutical compositions comprising these inhibitors, and methods of using these compositions for treatment and prevention of various disorders. *Id.* at Abstract.

63. The ’357 publication suggests that the diaryl urea structure is an important backbone of an inhibitor of a cell proliferation. Notably, the ’357 publication discloses a number of structures with a diaryl urea core and a chlorine para to the urea nitrogen. *See, e.g.*, Compound Nos. 1, 3, 4, 17, 18, 24, 45, 48, 49, 52, 56, 61, 62-64, 66, 68, 70, 72, 74, 76, 78, 81, 83, 85, 87, 89, 92, 93, 99, 101, 103, 105, 108-132, 135. ’357 at 59-85. Within a total of 139 disclosed compounds, over 42% contain the chloro-substituent para to the urea nitrogen, consistent with the structure of Winkler Compound I.

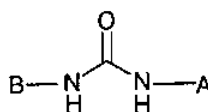
64. The ’357 publication also discloses a number of compounds consisting of an oxygen para to the urea nitrogen. *See, e.g.*, Compound Nos. 8, 9, 19-43, 59, 60, 68, 69, 78, 79, 83, 84, 103-106, 108, 109. This is consistent with the teachings of Armistead, the ’880 patent, the ’265 application, and PCT International Publication No. WO 99/32106 to Dumas, et al. (“Dumas PCT”), which disclose the oxygen in the same position. Finally, compound Nos. 24, 68, 78, 83, 103, 105, 108, and 109 disclose compounds that have the diaryl urea core, as well as both the chlorine and oxygen at the para positions to the urea nitrogens.

65. A number of the aforementioned compounds are specifically described as preferred compounds. *See, e.g.*, ’357 publication at 36: 3-9 (listing compound nos. 4, 22, 24, 25, 29-31, 33, 35, 64, and 105 as preferred compounds). The publication (*id.* at 8:12-18) further describes “an even more preferred embodiment” where **Z** is a 2,4,5-trisubstituted phenyl or **a 3,4-disubstituted phenyl, wherein the substituents are selected from halo, OR³, NO₂, NH₂, N(R³)₂, CO₂R³, CON(R³)₂, COR³, NHCOR³, SO₂NR³, CN, SR³, 1,2-methyleneoxy, 1,2-ethylenedioxy, CF₃ or (C₁-**

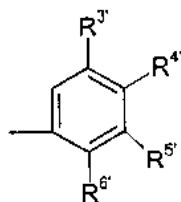
C₆)-straight or branched alkyl. *See also id.* at 6:20-25, disclosing **W** as a **phenyl** or pyridyl, each **containing up to 3 substituents selected from** halo, **OR³**, NO₂, NH₂, N(R³)₂, CO₂R³, CON(R³)₂, COR³, NHCOR³, SO₂NR³, CN, SR³, 1,2-methyleneoxy, 1,2-ethylenedioxy, CF₃ or (C₁-C₆) - straight or branched alkyl. R³ is selected from H, C₁-C₆ straight or branched alkyl, C₂-C₆ straight or branched alkenyl or alkynyl or **C₆₋₂₀ aryl**, wherein **R³ optionally contains up to 4 substituents selected from** halo, -OH, -OR₄, -NO₂, -NH₂, -N(R₄)₂, -CO₂R₄, **-CO-N(R⁴)₂**, -Z, -CN, -SR₄, CF₃ or -SO₂NR⁴ (R³ definition at 5:27-6:1) and **R⁴ is independently H, (C₁-C₆)-straight** or branched alkyl, (C₂-C₆)-straight or branched alkenyl or alkynyl (R⁴ definition at 6:2-4).

66. U.S. Patent Published Application 2008/0269265 to Miller, et al. ("Miller '265 publication") provides another example of the known raf kinase inhibition properties of the diaryl urea core. The Miller '265 publication describes symmetrical and unsymmetrical substituted diphenyl ureas useful for the treatment of a cancerous cell growth mediated by raf kinase. *Id.* at 25-41.

67. Miller's aryl ureas include both aryl and heteroaryl analogues, which inhibit the raf pathway. *Id.* at [0004]. Both types of ureas have the same structural backbone. Miller's ureas are illustrated as formula II:



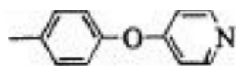
wherein, A can be a six member ring having the structure below



Id. at [0020], [0021].

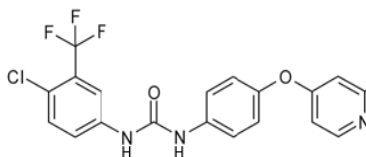
68. B can be substituted or unsubstituted, up to tricyclic aryl or heteroaryl moieties of up to 30 carbon atoms with at least one 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, where if B is substituted it is substituted by one or more substituents selected from the group consisting of halogen, up to per-halo, and W_n , wherein n is 0-3 and W is independently selected from many other groups. *Id.* at [0022].

69. In the 5 tables of the Miller '265 publication (*id.* at 25-41), Miller sets forth 144 substituted phenyl ureas, all of which are listed as displaying IC_{50} inhibitory concentration between 1 nM and 10 μ M for raf kinase. *Id.* at [0196]. Of Miller's 144 compounds, 22 are diaryl ether urea compounds also containing a 4-chloro-3-(trifluoromethyl)phenyl group similar in structure to Winkler's Compound I^a. *Id.* at Table 3. Of this group of 22 compounds, only compound 102 contains $R^2 = 4\text{-(4-pyridinyloxy)phenyl}$:



70. The R^2 substituent 4-(4-pyridinyloxy)phenyl of compound 102 is the most frequently deployed sidechain in the compounds disclosed in the Miller '265 publication and is a tested moiety in every compound permutation considered in Tables 1 and 2. In particular, in Table 1, compounds 9, 12, 17 and 25 contain this moiety; in Table 2, compounds 38, 81, 82 and 83 contain this moiety; in Table 3, compounds 102, 118, and 119 contain this moiety; and in Table 4, compounds 127, 132-141, and 144 contain this moiety.

71. In Table 3, the Miller '265 publication discloses Compound 102, a 4-chloro-3-(trifluoromethyl)phenyl urea having the structure below:



72. In method A16, the Miller '265 publication discloses carbamoyl substituted compounds and in A20, the Miller '265 publication discloses 2-(N-methylcarbamoyl)-4-chloropyridines, useful for synthesis of substituted anilines. *Id.* at [0151], [0152], [0161], [0162]. The Miller '265 publication also discloses a combinatorial method for synthesis of diphenyl ureas using triphosgene. *Id.* at [0186].

73. In addition to the compounds set forth in Miller's tables, the Miller '265 publication also teaches pharmaceutically acceptable salts including basic salts of inorganic and organic acids and acid salts of inorganic bases as follows:

The present invention is also directed to pharmaceutically acceptable salts of Formula I. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, sulphonic acid, acetic acid, trifluoroacetic acid, malic acid tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2} , Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Id. at [0044].

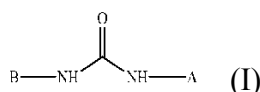
74. Miller's pharmaceutical compositions also include a compound of Formula I, and a physiologically acceptable carrier. *Id.* at [0004] and [0055]. Miller further discloses tablets containing the active ingredient as follows:

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable **excipients** which are suitable for the manufacture of tablets. These excipients may be, for example, inert **diluents**, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; **granulating and disintegrating agents**, for

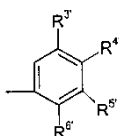
example, corn starch, or alginic acid; and **binding agents**, for example magnesium stearate, stearic acid or talc.

Id. at [0057] (emphasis added).

75. A similar reference is U.S. Patent No. 7,517,880 to Miller, et al. (“Miller ’880 patent”). Like the Miller ’265 publication, the Miller ’880 patent teaches diaryl asymmetric ureas which inhibit p38 mediated events including advanced cancer and cancer. (Miller ’880 patent at 4:29-36, 62-65) The ureas disclosed in the Miller ’880 patent are illustrated as formula I:



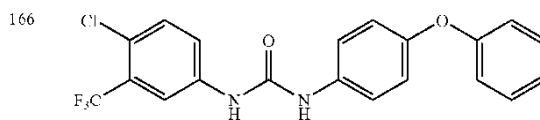
wherein, A can be a six member ring having the structure below



Id. at 5:25-47.

76. B can be substituted or unsubstituted, up to tricyclic aryl or heteroaryl moieties of up to 30 carbon atoms with at least one 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, where B is substituted it is substituted by one or more substituents selected from the group consisting of halogen, up to per-halo, and W_n, wherein n is 0-3 and W is independently selected from many other groups. *Id.* at col. 5: 25–62. These ureas can be used to inhibit p38 kinase and also routinely assayed for raf kinase activity, both implicated in cancer. *Id.* at 18:11-16, 5:16- 12:29. In short, the Miller ’880 patent discloses anti-cancer compounds.

77. In the 5 tables of the Miller ’880 patent (*id.* at 55-96), all compounds are listed as displaying IC₅₀ inhibitory concentration between 1 nM and 10 μM for p38 kinase. *Id.* at 97:1-2. In Table 5 of the Miller ’880 patent, among many miscellaneous ureas, there is Compound 166 which has the formula below:



Compound 166 has a structure that is closest to Winkler's Compound I^a.

78. Like the Miller '265 publication, the Miller '880 patent discloses carbamoyl substituted compounds useful for synthesis of substituted anilines (method A16) and 2-(N-methylcarbamoyl)pyridines (method A20). Miller '880 patent at 42:1-33, 44:15-51. The Miller '880 patent also discloses 2-(N-methylcarbamoyl)-4-chloropyridine. *Id.* at 44:15-51.

79. Therefore, the Miller '880 patent teaches a structure similar to sorafenib, wherein Compound 166 of the Miller '880 patent selected based on Winkler's Compound I^a structure but for a pyridine moiety bearing an N-methylcarbamoyl moiety on the 2-position. Moreover, the Miller '880 patent also teaches pharmaceutically acceptable salts including basic salts of inorganic and organic acids and acid salts of inorganic bases. *Id.* at 11:65- 12:20.

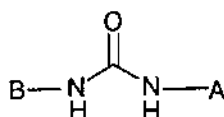
80. Miller's pharmaceutical compositions also include a compound of Formula I, and a physiologically acceptable carrier. *Id.* at 15:11-13. Miller further discloses tablets containing the active ingredient as follows:

Tablets contain the active ingredient in admixture with non-toxic pharmaceutically acceptable **excipients** which are suitable for the manufacture of tablets. These excipients may be, for example, inert **diluents**, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; **granulating and disintegrating agents**, for example, corn starch, or alginic acid; and **binding agents**, for example magnesium stearate, stearic acid or talc.

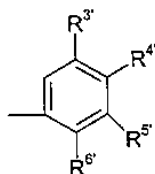
Id. at 15: 31-39 (emphasis added).

81. Another reference teaching the diaryl urea core's application in kinase inhibition is PCT International Publication No. WO 99/32436 to Miller, et al. ("Miller PCT"). Compound 102 depicts a raf kinase inhibitor that has the same structure as sorafenib, but for an N-methylcarbamoyl moiety on the 2-position of the pyridine ring. *Id.* at 70, Compound 102. More particularly, Miller PCT describes symmetrical and asymmetrical substituted diphenyl ureas useful

for the treatment of cancerous cell growth mediated by raf kinase. In short, Miller PCT discloses anti-cancer compounds. *Id.* at 2. Miller PCT's compounds are inhibitors of the raf kinase pathway. Miller discloses the p21^{ras} oncogene, a major contributor to the development and progression of human solid cancers, and that inhibiting raf kinase results in inhibiting active ras and thus, the inhibition of the growth of a variety of tumors. *Id.* Miller PCT's aryl ureas include both aryl and heteroaryl analogues, which inhibit the raf pathway. *Id.* Both types of ureas have the same structural backbone. Miller PCT's ureas are illustrated on page 5 as formula II:



wherein, A can be a six member ring having the structure below

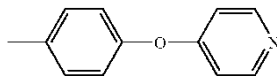


Id. at 5:1-4.

82. B can be substituted or unsubstituted, up to tricyclic aryl or heteroaryl moieties of up to 30 carbon atoms with at least one 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, where B is substituted it is substituted by one or more substituents selected from the group consisting of halogen, up to per-halo, and W_n, wherein n is 0-3 and W is independently selected from many other groups. *Id.* at 5:6-16.

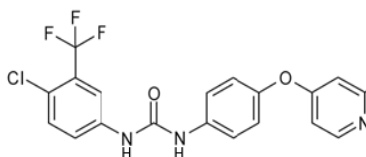
83. In his 5 tables (*id.* at 62-74), Miller PCT sets forth 144 substituted phenyl ureas, all of which are listed as displaying IC₅₀ inhibitory concentration between 1 nM and 10 μM for raf kinase. *Id.* at 74: 20. Of Miller PCT's 144 compounds 22 are diaryl ether urea compounds also containing a 4-chloro-3-(trifluoromethyl)phenyl group similar in structure to Winkler's Compound

1^a. *Id.* at Table 3 Of this group of 22 compounds, only compound 102 contains R² = 4-(4-pyridinyloxy)phenyl:



84. The R² substituent 4-(4-pyridinyloxy)phenyl of compound 102 is the most frequently deployed sidechain in the Miller PCT compounds and is a tested moiety in every compound permutation considered in Tables 1 and 2. In particular, in Table 1, compounds 9, 12, 17 and 25 contain this moiety; in Table 2, compounds 38, 81, 82 and 83 contain the R² moiety; in Table 3, compounds 102, 118, and 119 contain this moiety; and in Table 4, compounds 127, 132-141, and 144 contain this moiety.

85. In Table 3, Miller PCT discloses Compound 102, a 4-chloro-3-(trifluoromethyl)phenyl urea having the structure below:



Miller PCT's Compound 102 is almost the entire sorafenib structure but for an N-methylcarbamoyl moiety on the 2-position of the pyridine ring.

86. In methods A16 and A20 (*id.* at 46:9-26, 49:1-21), Miller PCT discloses carbamoyl substituted compounds useful for synthesis of substituted anilines (method A16) and 2-(N-methylcarbamoyl)pyridines (method A20). 2-(N-methylcarbamoyl)-4-chloropyridine disclosed by Miller PCT (*id.* at 49:1-21), is the same compound as 4-chloro-N-methyl-2-pyridinecarboxamide used in the '576 patent in the synthesis of sorafenib or compound 42 disclosed in the '576 patent ('576 patent at 46:16-20, 69). Miller PCT also discloses a combinatorial method for synthesis of diphenyl ureas using triphosgene. *Id.* at 59:4-17.

87. In addition to the compounds set forth in Miller PCT's tables, Miller PCT also teaches pharmaceutically acceptable salts including basic salts of inorganic and organic acids and acids salts of inorganic bases as follows:

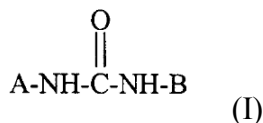
The present invention is also directed to pharmaceutically acceptable salts of Formula I. Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, phosphoric acid, methanesulphonic acid, trifluoromethanesulfonic acid, sulphonic acid, acetic acid, trifluoroacetic acid, malic acid tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, and mandelic acid. In addition, pharmaceutically acceptable salts include acid salts of inorganic bases, such as salts containing alkaline cations (e.g., Li^+ Na^+ or K^+), alkaline earth cations (e.g., Mg^{+2} , Ca^{+2} or Ba^{+2}), the ammonium cation, as well as acid salts of organic bases, including aliphatic and aromatic substituted ammonium, and quaternary ammonium cations such as those arising from protonation or peralkylation of triethylamine, *N,N*-diethylamine, *N,N*-dicyclohexylamine, pyridine, *N,N*-dimethylaminopyridine (DMAP), 1,4-diazabicyclo[2.2.2]octane (DABCO), 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

Id. at 9:9-23.

88. Miller PCT also teaches that the alleged invention also includes pharmaceutical compositions including a compound of Formula I, and a physiologically acceptable carrier. *Id.* at 13:8-9. Therefore, Miller PCT teaches a structure similar to sorafenib, but for the *N*-methylcarboxamide substituent on the 2-position of the pyridine ring.

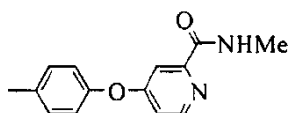
89. A further example of the diaryl urea core's role in raf kinase inhibition is Dumas PCT. As in Miller PCT, Dumas' compounds are asymmetrical substituted diaryl ureas that are useful to treat cancers by inhibiting raf kinase. Dumas PCT at 2:10:19. In particular, as described in Miller PCT's aryl ureas, Dumas PCT's aryl ureas include both aryl and heteroaryl analogues, which inhibit the raf pathway (Dumas PCT at 2:16-19) and are useful in treating solid cancers such as, for example, carcinomas (e.g., lungs, pancreas, thyroid, bladder or colon, myeloid disorders

(e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma)). *Id.* at 2: 11-14. Dumas PCT's ureas are illustrated as formula I:



(*id.* at 2:21), wherein B is generally an unsubstituted or substituted, up to tricyclic, aryl or heteroaryl moiety with up to 30 carbon atoms with at least one 5 or 6 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur. A is a heteroaryl moiety discussed in more detail below. *Id.* at 2:22-25.

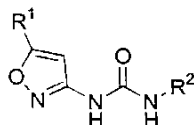
90. In Compound 101, R² is shown below:



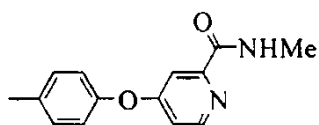
91. The R² moiety is a frequently tested moiety in almost every compound permutation considered in Dumas PCT's many tables. In particular, in Table 2 (*id.* at 93-101), compounds 182, 215, 218 and 261 contain this R² moiety. In Table 4 (*id.* at 106-108), compound 352 also contains this R² moiety. In Table 5 (*id.* at 109-111), compound 393 also contains this R² moiety.

92. Compound 101 would be considered by a POSA as a preferred compound. Dumas includes Compound 101, N-(5-tert-butyl-3-isoxazolyl)-N'-(4-(4-(2-methylcarbamoyl)pyridyl)oxyphenyl) urea, among specific examples of preferred 5-substituted-3-isoxazolyl urea compounds having the formula shown above. *Id.* at 13: 32-33.

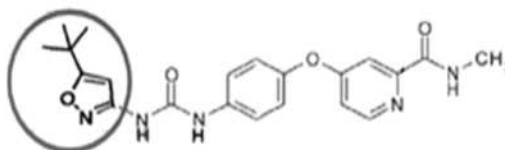
93. Compound 101, a 5-substituted-3-isoxazolyl urea has the structure below:



wherein R¹ is t-Bu (tert-butyl) and R² is



to yield Compound 101, which has a pyridine moiety bearing an N-methylcarbamoyl moiety on the 2-position. to provide the following structure:



Id. at 87, Table 1.

94. Dumas PCT's Compound 101 is similar to sorafenib but for a 4-chloro-3-(trifluoromethyl)phenyl substituent at the B position of the A-D-B backbone of the '576 patent, Dumas PCT has a 5-tertbutyl-3-isoxazolyl group as shown above in the circle. *Id.* at *Id.* at 87, Table 1. Like Miller PCT, all of Dumas PCT's compounds are listed as displaying IC₅₀ inhibitory concentration for raf kinase of between 1 nM and 10 μ M. *Id.* at 112: 4.

95. In methods B6 and B10 (*id.* at 52:20-53:8, 55:11-56:2), Dumas PCT discloses carbamoyl substituted compounds useful for synthesis of substituted anilines (method B6) and 2-(N-methylcarbamoyl)pyridines (method B10). Dumas PCT further discloses 2-(N-methylcarbamoyl)-4-chloropyridine. *Id.* In method C8, Dumas PCT also discloses combinatorial methods for the synthesis of diphenyl ureas using triphosgene via the same method disclosed in Miller PCT. *Id.* at 70:12-24. Therefore, the synthesis method of sorafenib is disclosed in Dumas PCT as well.

96. Like Miller PCT, in addition to the compounds set forth in Dumas PCT's tables, Dumas PCT also teaches pharmaceutically acceptable salts including basic salts of inorganic and organic acids and acids salts of inorganic bases (*id.* at 18:1-16). Further, like Miller PCT, Dumas PCT teaches that the alleged invention also includes pharmaceutical compositions that include compounds described above and a physiologically acceptable carrier. *Id.* at 17:8-9.

VI. LEGAL STANDARDS

a. Person of Ordinary Skill in the Art

97. Mylan's counsel has explained to me that many issues in patent law, including enablement, written description, anticipation, and obviousness, are determined from the perspective of a hypothetical POSA is presumed to have known the relevant art at the time of the invention.

98. I understand from Mylan's counsel that several factors may be considered in determining the level of ordinary skill in the art, including: (1) the type of problems encountered in the prior art; (2) the solutions to those problems in the prior art; (3) the rapidity with which innovations are made; (4) the sophistication of the technology; and (5) the educational level of active workers in the field of the invention.

99. A POSA for purposes of this report, as of January 13, 1999, which I understand to be the priority dates for the '834 and '623 patents and January 12, 2001, which I understand to be the priority date for the '576 patent, would have been an individual with a high level of education and skill, including an M.D. and/or a Ph.D. and at least two years of specialized experience in the area of treating solid tumors. The individual would have a substantive understanding of at least one of the following interdisciplinary fields: medicine, medicinal chemistry, pharmaceutical drug product development, organic chemistry, analytical chemistry, pharmacokinetics, biology, and any other related field.

100. I further understand that Plaintiffs contend that the claimed subject matter of the '834 and '623 patents was conceived no later than April 8, 1998. Regardless of whether this invention date has been properly established, my opinion as provided in this report would be equally applicable to this contended conception date.

101. I have been asked by counsel for Defendant to provide my expert opinion on the validity of the asserted claims, from the perspective of a POSA. My opinions as they relate to invalidity are the same under either the Defendant's or Plaintiffs' definition of a POSA.

b. Prior Art

102. Mylan's counsel has explained to me that prior art is what is known in the art at the time of the invention, i.e., as of the priority date of the patent. I understand from Mylan's counsel that a patent is entitled to a priority date that is as early as the date of its filing. Mylan's counsel has further explained to me that a patent may be entitled to the benefit of the filing date of an earlier application so long as certain legal criteria are met.

c. 35 U.S.C. § 103 – Obviousness

103. Mylan's counsel has explained to me that a patent is invalid where the differences between the patent claims and the prior art are such that the claimed invention, as a whole, would have been obvious to a POSA in the art at the time of the invention. In analyzing the question of obviousness, I have been asked by Mylan's counsel to consider the following: (1) the scope and content of the prior art; (2) the differences between the prior art and the claims at issue; and (3) the level of skill in the prior art.

104. I understand from Mylan's counsel that a claim may be obvious if it is a predictable improvement or combination of prior art elements according to their established functions. Mylan's counsel has explained to me that a combination of prior art elements is predictable where the prior art provides teaching, suggestion, or motivation to combine the references in such a way as to give a POSA a reasonable expectation of success in arriving at the claimed subject matter.

105. I understand from Mylan's counsel that a *prima facie* case of obviousness, i.e., obvious on its face, arises when a POSA merely pursues known options from a finite number of identified, predictable solutions.

106. I understand from Mylan's counsel that in determining what would have been obvious, I may take into account the inferences and ordinary creativity that a POSA would employ.

107. Mylan's counsel has explained to me that a single, obvious species renders the claimed genus invalid as obvious.

108. Mylan's counsel has also explained to me that an entire Markush-type claim, in a format such as "selecting the group consisting of A, B, and C," is invalid as obvious if the prior art renders the combination with, e.g., element C obvious to a person of skill in the art.

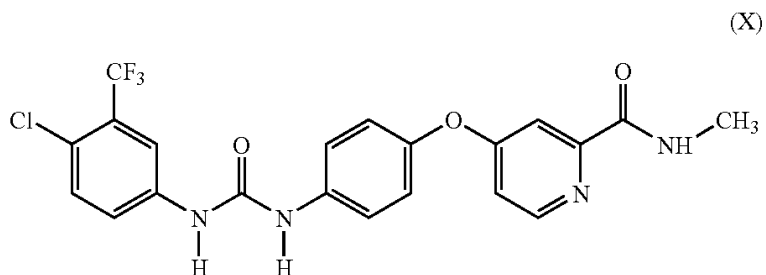
VII. INVALIDITY OPINIONS

a. Invalidity of the '834 Patent

i. The Asserted Claims of the '834 Patent

109. It is my understanding that Plaintiffs have asserted claims 39-41 of the '834 patent against Defendants.

110. Claim 39 of the '834 patent recites the compound sorafenib, having the structure set forth below, or a pharmaceutically acceptable salt thereof:



111. Claim 40 of the '834 patent, which depends from claim 39, further includes the limitation that the pharmaceutically acceptable salt of the sorafenib compound is a basic salt of an organic acid or an inorganic acid which is hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, trifluoromethanesulfonic acid, benzenesulfonic acid, p-toluene sulfonic acid (tosylate salt), 1-naphthalene sulfonic acid, 2-naphthalene sulfonic acid, acetic acid, trifluoroacetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid, or mandelic acid.

112. Claim 41 of the '834 patent, which also depends from claim 39, further includes a limitation that the sorafenib compound is a tosylate salt.

ii. Claims 39-41 of the '834 Patent Would Have Been Obvious to a POSA at the Time of the Invention

113. It is my opinion that claims 39-41 of the '834 patent are obvious in view of the prior art available at the time of the invention.

iii. Claim 39 of the '834 patent would have been obvious to a POSA in view of Winkler, Haga and Compound Optimization.

114. Winkler discloses Compound I^a, an asymmetrical substituted urea compound having a 4-chloro-3-(trifluoromethyl)phenyl group and a substituted phenoxyphenyl group which can inhibit CoA-IT by blocking cancer cells proliferation. Compound I^a is the only urea described which causes apoptosis (antiproliferative activity against cancer cells), while the other diaryl urea, compound II^b was found to be inactive and not capable of inducing cell apoptosis. Winkler at 11, Table 1.

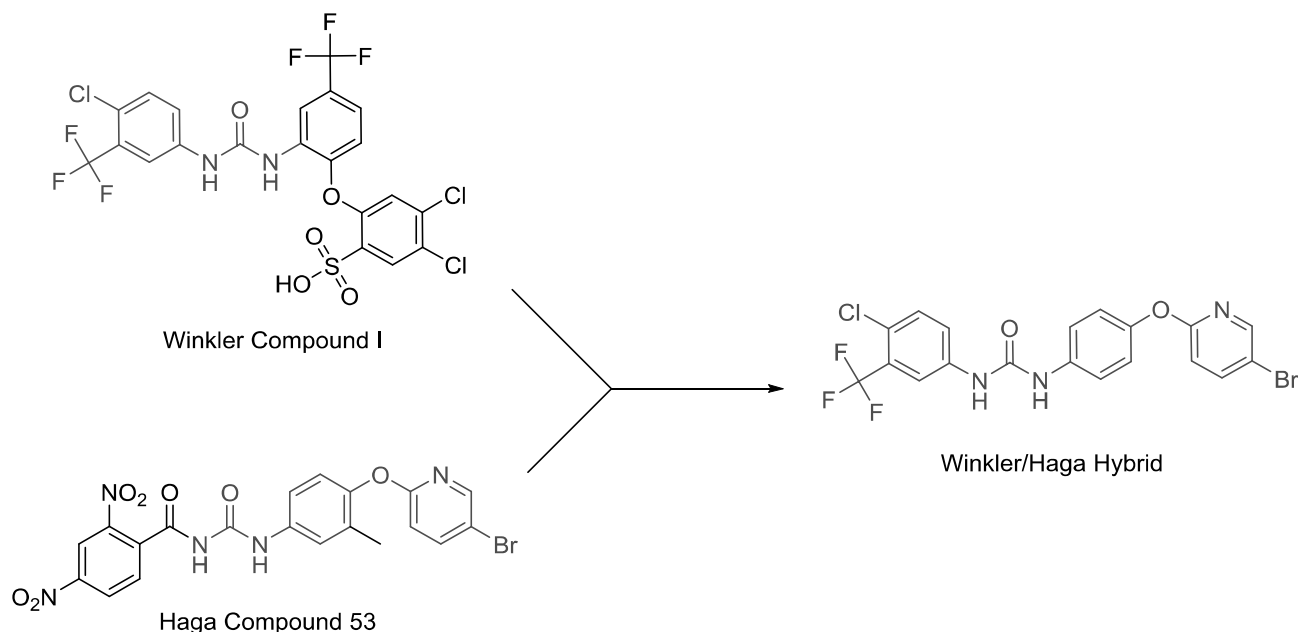
115. At the time of the invention, it was also known that urea compounds have broad tyrosine kinase inhibition activity. '325 publication at 137:17-24. Accordingly, it is my opinion that a POSA seeking to provide a lead compound with potential antiproliferative activity would select for further investigation the only ureido compound that can induce cell apoptosis disclosed in Winkler, namely Compound I^a.

116. Haga discloses Compound 53 as the closest structure to Winkler's Compound I^a. Like Winkler, Haga's Compound 53 has antiproliferative properties. Haga notes that the disclosed compounds may have poor solubility. *See* Haga at 26:3-4, Compound 53.

117. It is my opinion that a POSA would test the resulting hybrid for anti-cancer activity. It is also my opinion that to design a urea, compound with anti-cancer activity, a POSA would have found it obvious to make sorafenib by taking Winkler's Compound I^a and modifying it in view of Haga's Compound 53, which has superior anti-cancer activity as evidenced by its high increase life span (ILS) (Haga at Table 5), against cancerous cells.

118. Further, it is my opinion that a POSA would have a reasonable expectation of success because Compound I^a could induce apoptosis of cancerous cells at 50 μ M. Winkler at 11,

Table 1. It is my understanding that Haga's Compound 53 would be recommended by its high ILS value against leukemia cells. As such, it is my opinion that a POSA would combine the Winkler and Haga compounds to obtain a Winkler-Haga hybrid as illustrated below:

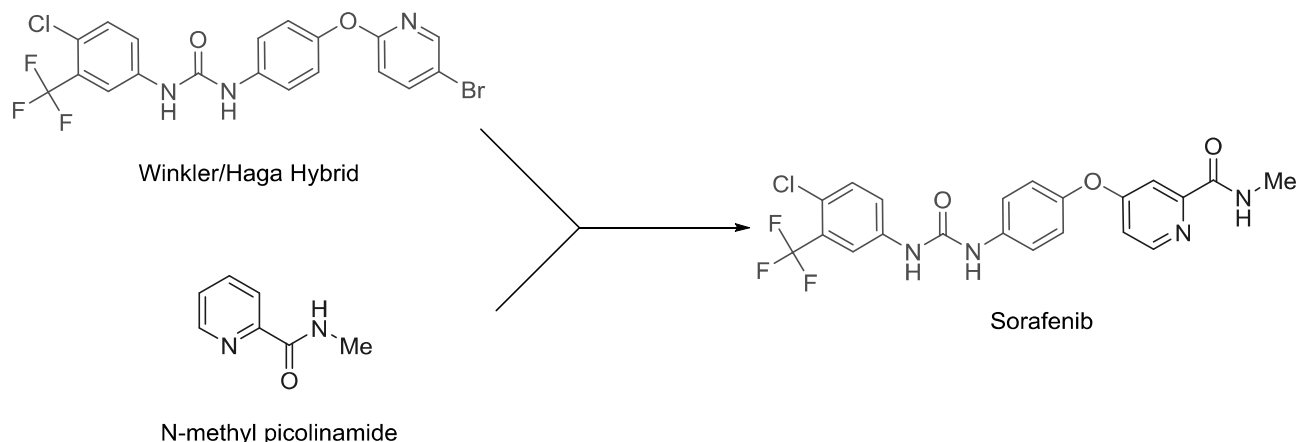


119. Because Haga also teaches that his disclosed compounds disclosed are poorly soluble and their solubility should be optimized, it is also my opinion that a POSA would try to improve the compound's solubility. *Id.* at 26:3-4.

120. It was also known in the art since 1989 that diphenyl ureas have poor solubility. *See* Haga at 26:3-4, Compound 53. It was further known that nicotinamide and picolinamide have high solubility in water. N-Methylpicolinimide, which in my opinion is an obvious derivative of picolinamide, would have been an obvious modification of the Miller '265 publication's Compound 102, which could be used by a POSA to enhance the solubility and bioavailability of a raf kinase inhibitor while potentially improving its potency as a raf kinase inhibitor binding to the enzyme receptor pocket. As such, a POSA would know that incorporating an N-methylcarboxamide into Haga Compound 53 would enhance solubility and bioavailability while potentially improving its potency as a raf kinase inhibitor binding to the enzyme receptor pocket.

Incorporating N-methylcarboxamide into pyridine group would result in the sorafenib structure.

The resulting structure is depicted below:



121. For at least these reasons, it is my opinion that claim 39 of the '834 patent is invalid as obvious under 35 U.S.C. § 103(a) over the prior art of Winkler in view of Haga and the compound optimization techniques that would encourage the incorporation of N-methylpicolinamide.

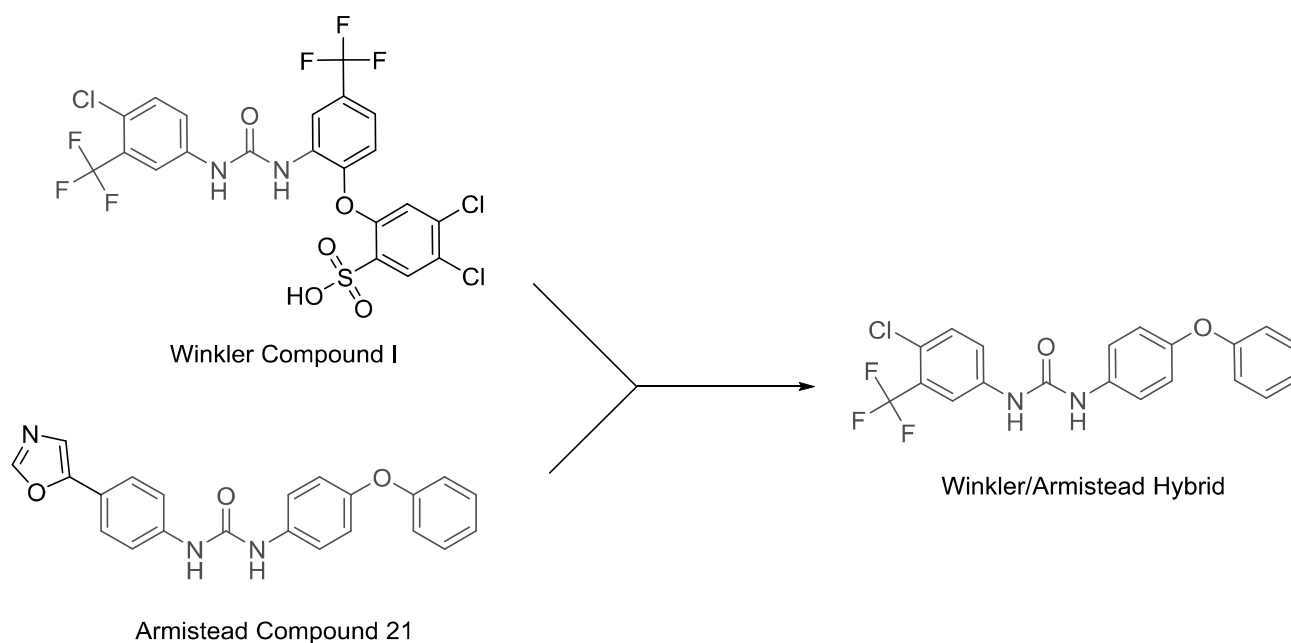
iv. Claim 39 of the '834 patent would have been obvious to a person of skill in the art in view of Winkler, Armistead and Compound Optimization.

122. As discussed above, the selection of Winkler's urea Compound I^a was known in the prior art at the time of invention.

123. As discussed above, Armistead discloses Compound 21, preferably used to inhibit tumors and cancer in a mammal. Armistead at 43: 21-26.

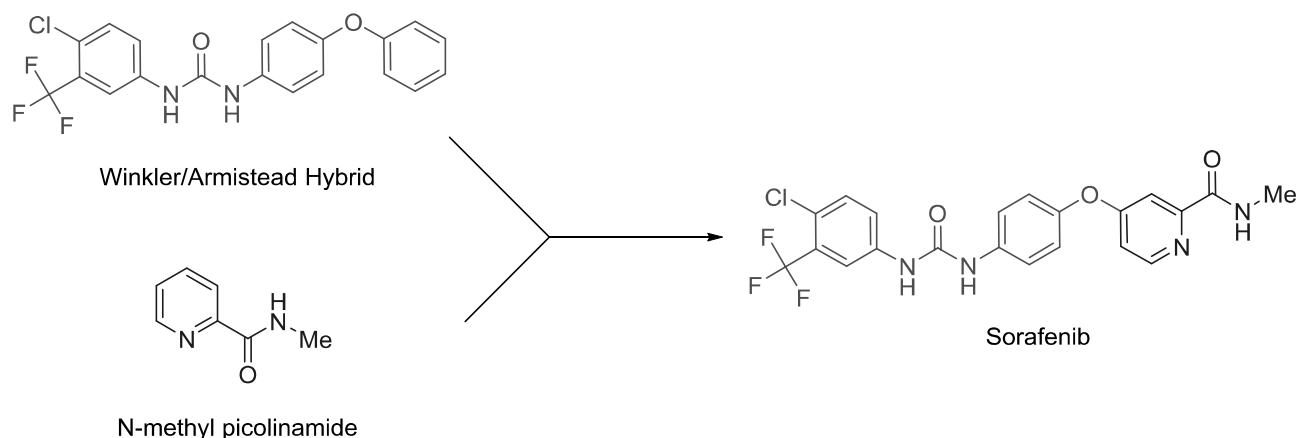
124. Based on this structural similarity and because it was known to inhibit cancerous tumors, it is my opinion that starting with Winkler's Compound I^a, a POSA would consider Armistead Compound 21.

125. It is my opinion that to design a urea compound with anti-cancer activity, a POSA would find it obvious to make sorafenib by taking Winkler's Compound I^a and modify it in view of Armistead Compound 21 to obtain a Winkler-Armistead hybrid, especially in view of their structural similarity:



126. Armistead also provides that the compounds disclosed therein may be modified to increase their solubility. *Id.* at 32:27-33:3. As such, it is my opinion that a POSA would try to improve the solubility of the Winkler-Armistead hybrid and potentially improve the compound's ability to bind to an enzyme receptor and thus inhibit the growth of cancer cells. Optimizing the lead compound as described above by replacing one of the phenyl groups with N-methylpicolinamide would result in the sorafenib structure or structures for which sorafenib would be an obvious variant, as discussed above.

127. Accordingly, it is my opinion that incorporating N-methylpicolinamide into the Winkler-Armistead hybrid would enhance its solubility resulting in better bioavailability and enhanced binding to an enzyme receptor pocket. The resulting structure is depicted below:

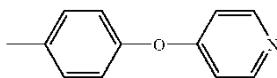


128. For at least these reasons, it is my opinion that claim 39 of the '834 patent are invalid as obvious under 35 U.S.C. § 103(a) over the prior art of Winkler in view of Armistead and the compound optimization techniques that would encourage the incorporation of N-methylpicolinamide.

v. Claim 39 of the '834 patent would have been obvious to a person of skill in the art in view of Winkler, the Miller '265 publication and Compound Optimization

129. As discussed above, the selection of Winkler's urea Compound I^a was known in the prior art at the time of invention.

130. As also described above, the Miller '265 publication discloses anti-cancer compounds, including Compound 102, which contains R² = 4-(4-pyridinyloxy)phenyl:



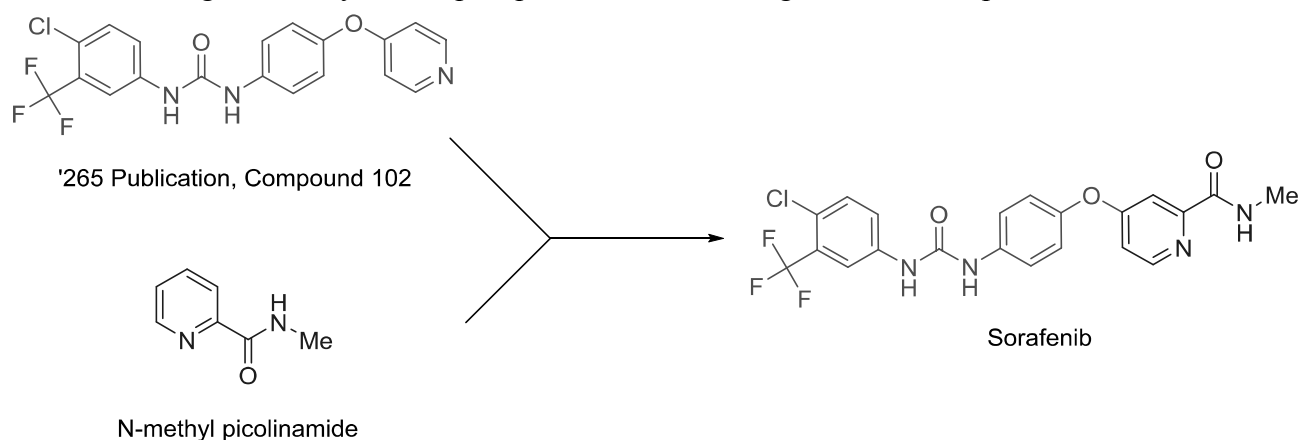
Because 4-(4-pyridinyloxy)phenyl, as used in the 102 compound, is the most tested in every compound permutation of Tables 1 and 2 of the Miller '265 publication, it is my opinion that Compound 102 emerges as the natural lead compound

131. Furthermore, Miller '265 para.[0162]-[0163] discloses the synthesis of 2-(N-methylcarbamoyl)-4-chloropyridine, which is the same compound as 4-chloro-N-methyl-2-

pyridinecarboxamide which was used in the '834 patent in the synthesis of sorafenib (compound 42) disclosed in the '834 patent (*id.* at 49:24-28, 15:1-16:17). The Miller '265 publication also discloses a combinatorial method for synthesis of diphenyl ureas using triphosgene which is similar to a method utilized in the '834 patent for the same purpose. Miller '265 publication at [0185]; '834 patent at 39:20, et seq.

132. It is my opinion that the Miller '265 Publication's Compound 102 has more than a mere structural similarity to sorafenib; it is recognized as a potent raf kinase inhibitor having an IC_{50} of between 1nM and 10 μ M used for the treatment of cancerous cell growth mediated by raf kinase. *Id.* at [0020], [0196].

133. As discussed above, the effectiveness of a drug candidate depends heavily upon optimizing potency and bioavailability, which in turn includes considerations of solubility and permeability. As such, it is my opinion that a person of ordinary skill in the art would have known that incorporating N-methylpicolinamide, shown in blue, into the Winkler-Miller '265 Publication hybrid would enhance its solubility resulting in better bioavailability and would potentially enhance binding to an enzyme receptor pocket. The resulting structure is depicted below:



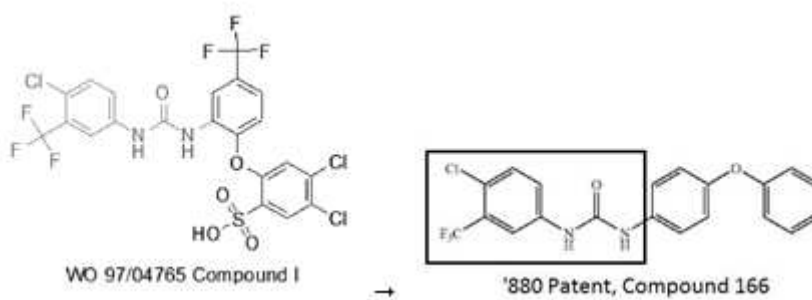
134. For at least these reasons, it is my opinion that claim 39 of the '834 patent is invalid as obvious under 35 U.S.C. § 103(a) over the prior art of Winkler in view of the the Miller '265 publication and the compound optimization provided by N-methylpicolinamide with its ability to

potentially enhance solubility and bioavailability while potentially improving its potency as a raf kinase inhibitor binding to the enzyme receptor pocket.

vi. Claim 39 of the '834 patent would have been obvious to a person of skill in the art in view of Winkler, the Miller '880 patent and Compound Optimization

135. As discussed above, the selection of Winkler's urea Compound I^a was known in the prior art at the time of invention.

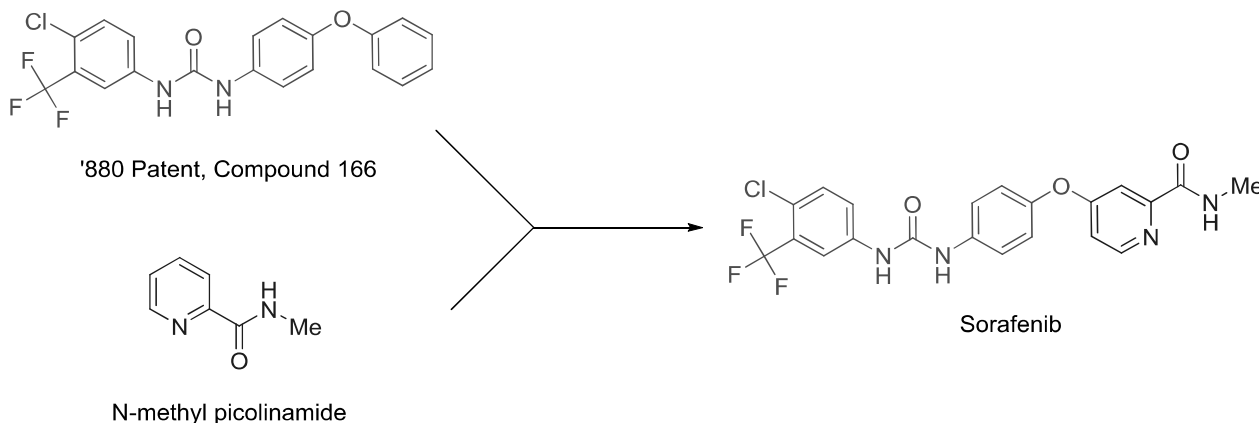
136. The Miller '880 patent discloses the Compound 166 in Table 5, which is the only unsymmetrical Miller urea compound that has trifluoromethyl and chloro moieties on one of its phenyl groups, a structure similar to Winkler's Compound I^a as depicted below:



137. Additionally, 2-(N-methylcarbamoyl)-4-chloropyridine which is disclosed by Miller, '880 para. [0162]-[0163] is the same compound as 4-chloro-N-methyl-2-pyridinecarboxamide used in the '834 patent in the synthesis of sorafenib or compound 42 disclosed in the '834 patent (*id.* at 49:24-28). As such, it is my opinion that, to design a urea compound with anti-cancer activity, a POSA would have found it obvious to make sorafenib by using Winkler's Compound I^a to select the Miller '880 patent's Compound 166.

138. As discussed above, the effectiveness of a drug candidate depends heavily upon optimizing potency and bioavailability, which in turn includes considerations of solubility and permeability. As such, it is my opinion that a person of ordinary skill in the art would have known that incorporating N-methylpicolinamide, shown in blue, into the Winkler-Miller '880 Patent

hybrid would enhance its solubility resulting in better bioavailability and would potentially enhance binding to an enzyme receptor pocket. The resulting structure is depicted below:



139. For at least these reasons, it is my opinion that claim 39 of the '834 patent are invalid as obvious under 35 U.S.C. § 103(a) over the prior art of Winkler in view of the Miller '880 patent and the compound optimization techniques that would encourage the incorporation of N-methylpicolinamide.

vii. Claim 39 of the '834 Patent Would Have Been Obvious to Try by a POSA at the Time of the Invention

140. It is my opinion that the modification of Winkler-Haga, Winkler-Armistead, Winkler-Miller '265 publication, or Winkler-Miller '880 patent to make sorafenib would have been obvious to try to a POSA.

141. As discussed above, both the Miller '265 publication and the Miller '880 patent disclosed N-methylcarbamoyl substituted pyridines used in the preparation of sorafenib. Also as discussed above, in connection with at least the Miller '265 publication, the inventors were familiar with combinatorial methods of diphenyl ureas using triphosgene, which is similar to a method of preparing sorafenib disclosed in the '834 patent. Based on this information, it is my opinion that the inventors of the '834 patent were familiar with combinatorial methods of synthesis for the development of a library of potential lead compounds whose structure-activity relationship (SAR)

could be further explored vis-à-vis their anti-cancer potency and these compounds could be routinely optimized. Miller '265 publication at [0185].

142. Additionally, the desire to provide drug-like lead compounds having increased bioavailability while preserving anti-cancer potency and increasing enzyme binding activity provides a motivation and reasonable expectation of success for adding N-picolinamide on the hybrid structures discussed above or adding an N-methylcarbamoyl moiety on the pyridine ring of Miller's compounds 102 or 166 as taught by Data from SRC PhysProp Database for N-methylpicolinamide. *See* Lipinski at 4-9; Curatolo at 390-391; Haga at 26:3-6.

143. For at least these reasons, it is my opinion that claim 39 of the '834 patent is invalid as obvious to try.

viii. Admissions by Inventors in Later Publications and in the '834 Patent Further Support a Finding of Invalidity Under 35 U.S.C. § 103 as Obvious

144. It is my opinion that admissions by inventors in later publications further show that the development of sorafenib was the result of routine optimization and thus obvious. For example, the inventors describe how their knowledge and use of combinatorial chemistry led to the routine "optimization" of the lead compound which led to a series of a clinical candidate BAY 93-9006, which is Sorafenib. *See* Khire at 783-786.

145. It is my understanding that the inventors also acknowledge that in 1994, when a team was assembled to develop sorafenib, the introduction and refinement of in vitro HTS and combinatorial chemistry greatly facilitated the development of new chemicals. It is my opinion that, an assay for HTS identification of selective Raf/MEK/ERK enzyme inhibitors discovered by Glaxo-Wellcome was vital in identifying and selecting candidate raf kinase inhibitors for further evaluation for Phase 1 clinical trials. *See* Wilhelm at 835-844.

146. Accordingly, it is my opinion that using HTS, ADME (absorption, distribution, metabolism, and excretion) and known assay technologies to determine toxicology of various asymmetric ureas known as raf kinase inhibitors, the selection of the Miller '265 publications's

Compound 102 as a lead compound and modifying it with an N-methylpicolinamide would have been obvious to try and mere routine optimization, as acknowledged by the inventors in the Wilhelm and Khire publications.

147. Further, in the '834 patent, the Applicants stated that "[t]he activity of a given compound to inhibit raf kinase can be routinely assayed, e.g., according to procedures disclosed below." '834 patent at 9:43-45.

148. Accordingly, it is my opinion that sorafenib as claimed in claim 39 of the '834 patent would have been obvious under 35 U.S.C. § 103 and therefore invalid over a combination of the Miller '265 publication's Compound 102 and 2-pyridinecarboxamide as it would have been obvious to a POSA to screen these compounds at the time of the alleged invention to test their raf kinase activity, as it would be routine optimization.

ix. Asserted Claims 40-41 of the '834 Patent Would Have Been Obvious to a POSA at the Time of the Invention

149. Independent claim 39 recites sorafenib generically or as a specie. Claim 40 depends from claim 39 and therefore incorporate the limitations of the independent claim. Moreover, claim 40 also recites an acceptable salt of a given list. Armistead teaches pharmaceutically acceptable salts of his compounds including those derived from pharmaceutically acceptable inorganic and organic acids, also including both acid salts and basic salts. Armistead at 29:1-28. Based on my understanding that when a claim covers several compositions, the claim is obvious if one of them is taught in the prior art, claim 40 is invalid under 35 U.S.C. § 103(a) as obvious over the prior art of (i) Winkler in view of Haga, (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; (iv) Winkler in view of the Miller '880 patent, all in combination with N-methylpicolinamide for the same reasons as discussed above with respect to claim 1.

150. Claim 41 depends on claim 39 with the added limitation of the tosylate salt of sorafenib. Armistead teaches antiproliferative urea compounds and their pharmaceutically acceptable salts derived from pharmaceutically acceptable inorganic and organic acids also

including tosylate. Armistead at 29:1-28. Pharmaceutically acceptable salts of Armistead's compounds include salts of inorganic or organic acids, e.g., *inter alia*, acetate, maleate, as well as tosylate and base salts, e.g., alkaline metal salts and the like. *Id.* It is my opinion that a POSA, seeking to provide pharmaceutically acceptable salts of organic acids of the sorafenib compound as taught by (i) Winkler in view of Haga, (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; (iv) Winkler in view of the Miller '880 patent, in combination with N-methylpicolinamide would produce the tosylate salt of Armistead as part of routine optimization based on a reasonable expectation of success. As such, it is my opinion that making an active compound into a particular salt form such as tosylate is not inventive as it does not have any effect on its therapeutic efficacy.

151. Additionally, Armistead disclosed a tosylate as a known pharmaceutical salt of antiproliferative urea compounds. As such, it is my opinion that a POSA would find it obvious and have a reasonable expectation of success in producing the tosylate of sorafenib as taught by (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with N-methylpicolinamide in further view of Armistead.

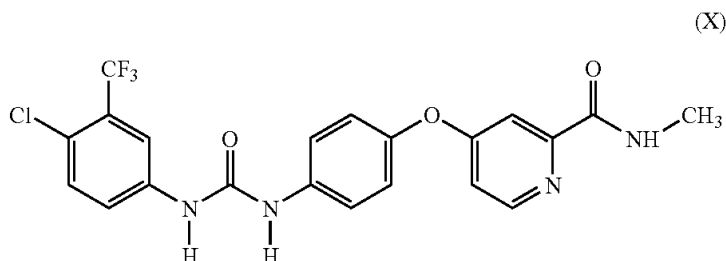
152. For at least these reasons, it is my opinion that claims 39-41 of the '834 patent are invalid as obvious under 35 U.S.C. § 103(a) over the prior art of (i) Winkler in view of Haga, (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; (iv) Winkler in view of the Miller '880 patent, all in combination with N-methylpicolinamide.

b. Invalidity of the '623 Patent

i. The Asserted Claims of the '623 Patent

153. It is my understanding that Plaintiffs have asserted claims 1-6 of the '623 patent against Defendants.

154. Claim 1 of the '623 patent recites the compound of sorafenib, having the structure set forth below, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier:



155. Claim 2 of the '623 patent, which depends from claim 1, further includes the limitation that the pharmaceutically acceptable salt thereof is a tosylate salt.

156. Claim 3 of the '623 patent recites the compound of sorafenib, having the structure set forth above, or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier.

157. Claim 4 of the '623 patent, which depends from claim 3, further includes the limitation that the pharmaceutically acceptable salt thereof is a tosylate salt.

158. Claim 5 of the '623 patent recites the tablet of sorafenib, having a structure set forth above, or a pharmaceutically acceptable salt thereof, and at least one pharmaceutically acceptable excipient.

159. Claim 6 of the '623 patent, which depends from claim 5, further includes the limitation that the pharmaceutically acceptable salt thereof is a tosylate salt.

ii. Claims 1-6 of the '623 Patent Would Have Been Obvious to a POSA at the Time of the Invention

160. It is my opinion that claims 1-8 of the '623 patent are obvious in view of the prior art available at the time of the invention.

iii. Claim 1 of the '623 patent would have been obvious in view of the prior art of Winkler, Haga and Compound Optimization

161. It is my opinion that claim 1 of the '623 patent would have been obvious to a POSA in view of Winkler, Haga, and compound optimization for the reasons explained above for the '834 patent.

iv. Claim 1 of the '623 patent would have been obvious in view of the prior art of Winkler, Armistead and Compound Optimization

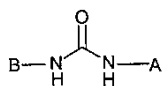
162. It is my opinion that claim 1 of the '623 patent would have been obvious to a POSA in view of Winkler, Armistead, and compound optimization for the reasons explained above for the '834 patent.

v. Claim 1 of the '623 patent would have been obvious in view of the prior art of Winkler, the Miller '265 publication and Compound Optimization

163. It is my opinion that claim 1 of the '623 patent would have been obvious to a POSA in view of Winkler, the Miller '265 publication, and compound optimization for the reasons explained above.

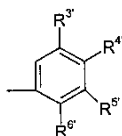
164. In addition, like the '623 patent, the Miller '265 publication describes symmetrical and unsymmetrical substituted diphenyl ureas useful for the inhibition of raf kinase. Miller '265 publication at 25-41. Like the '623 patent (4:35-39, 5:28 – 7:42), the Miller '265 publication's aryl ureas include both aryl and heteroaryl analogues, which inhibit the raf pathway (*id.* at [0004]).

Both types of ureas have
illustrated as formula II:



aryl backbone. The Miller '265 publication's urea are
wherein, A can be a six member ring having the structure

below:



Id. at [0020], [0021].

165. In the above image, B can be substituted or unsubstituted, up to tricyclic aryl or heteroaryl moieties of up to 30 carbon atoms with at least one 6-member aromatic structure

containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, where B is substituted, it is substituted by one or more substituents selected from the group consisting of halogen, up to per-halo, and W_n, wherein n is 0-3 and W is independently selected from many other groups. *Id.* at [0022]. The '623 patent has the same backbone structure.

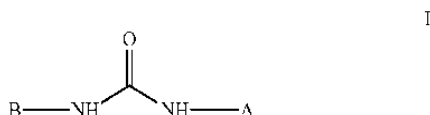
166. Additionally, in methods A16 and A20, the Miller '265 publication discloses carbamoyl substituted compounds useful for synthesis of substituted anilines (method A16) and 2-(N-methylcarbamoyl)pyridines (method A20). *Id.* at [0151], [0152], [0161], [0162]. 2-(N-methylcarbamoyl)-4-chloropyridine disclosed in the Miller '265 publication (*id.* at [0162]), is the same compound as 4-chloro-N-methyl-2-pyridinecarboxamide used in the '623 patent in the synthesis of sorafenib or compound 42 disclosed in the '623 patent (*id.* at id at 18:26 - 21:16). The Miller '265 publication also discloses a combinatorial method for synthesis of diphenyl ureas using triphosgene which is similar to a method utilized in the '623 patent for the same purpose. Miller '265 publication at [0185]; '623 patent at 18:26 - 21:16, et seq.

167. For at least these reasons, it is my opinion that claim 1 of the '623 patent is invalid as obvious under 35 U.S.C. § 103(a) over the prior art of Winkler in view of the Miller '265 publication and the compound optimization techniques that would encourage the incorporation of N-methylpicolinamide.

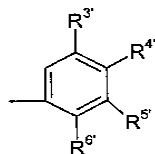
vi. Claim 1 of the '623 patent would have been obvious in view of the prior art of Winkler, the Miller '880 patent and Compound Optimization

168. It is my opinion that claim 1 of the '623 patent would have been obvious to a POSA in view of Winkler, the Miller '880 patent, and compound optimization for the reasons explained in section III.a.ii.4.

169. Specifically, like the Miller '265 publication, the Miller '880 patent teaches the ureas disclosed in the Miller '880 patent as formula I:



wherein, A can be a six member ring having the structure below:



Miller '880 patent at 5:22-48.

170. In the above image, B can be substituted or unsubstituted, up to tricyclic aryl or heteroaryl moieties of up to 30 carbon atoms with at least one 6-member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur, where B is substituted, it is substituted by one or more substituents selected from the group consisting of halogen, up to per-halo, and W_n , wherein n is 0-3 and W is independently selected from many other groups. *Id.* at 5:25-62. These ureas can be used to inhibit p38 kinase and also raf kinase. *Id.* at 18:11-12.

171. The '623 patent has the same backbone structure. In the five tables of the Miller '880 patent, all compounds are listed as displaying IC50 inhibitory concentration between 1nM and 10 μ M for raf kinase. *Id.* at 97:1-2.

172. Like the Miller '265 publication, the Miller '880 patent discloses carbamoyl substituted compounds useful for synthesis of substituted anilines (method A16) and 2-(N-methylcarbamoyl)pyridines (method A20). *Id.* at 42:1-34, 44:15-51. 2-(N-methylcarbamoyl)-4-chloropyridine disclosed in the Miller '880 patent is the same compound as 4-chloro-N-methyl-2-pyridinecarboxamide used in the '623 patent in the synthesis of sorafenib or compound 42 disclosed in the '623 patent (*id.* at id at 18:26 - 21:16).

173. For at least these reasons, it is my opinion that claim 1 of the '623 patent are invalid as obvious under 35 U.S.C. § 103(a) over the prior art of Winkler in view of the Miller '880 patent and the compound optimization techniques that would encourage the incorporation of N-methylpicolinamide.

vii. Claim 1 of the '623 Patent Would Have Been Obvious to Try a POSA at the Time of the Invention

174. It is my opinion that the modifications of Winkler-Haga or Winkler-Armistead, Winkler-Miller '265 publication, Winkler-Miller '880 patent to make sorafenib would have been obvious to try to a POSA at the time of invention and, therefore, claim 1 of the '623 patent is invalid. I incorporate by reference the opinions provided above for the '834 patent.

viii. Admissions by Inventors in Later Publications and in the '834 Patent Further Support of Finding of Invalidity Under 35 U.S.C. § 103 as Obvious

175. It is my opinion that admissions by inventors in later publications further show that the development of sorafenib was the result of routine optimization and thus obvious. For example, the inventors describe how their knowledge and use of combinatorial chemistry led to the routine "optimization" of the lead compound which led to a series of a clinical candidate BAY 93-9006, which is Sorafenib. *See Khire* at 783-786.

176. It is my understand that the inventors also acknowledge that in 1994, when a team was assembled to develop sorafenib, the introduction and refinement of in vitro HTS and combinatorial chemistry greatly facilitated the development of new chemicals. It is my opinion that, an assay for HTS identification of selective Raf/MEK/ERK enzyme inhibitors discovered by Glaxo-Wellcome was vital in identifying and selecting candidate raf kinase inhibitors for further evaluation for Phase 1 clinical trials. *See Wilhelm* at 835-844.

177. Accordingly, it is my opinion that using HTS, ADME (absorption, distribution, metabolism, and excretion) and known assay technologies to determine toxicology of various asymmetric ureas known as raf kinase inhibitors, the selection of the Miller '265 publication's Compound 102 as a lead compound and modifying it with an N-methylpicolinamide would have been obvious to try, and mere routine optimization as acknowledged by the inventors in the Wilhelm and Khire publications.

178. Additionally, as Applicants admitted in the '623 patent, since inhibition against raf kinase lead to inhibition against p38 kinase, testing sorafenib's anti-cancer potency by inhibiting p38 kinase was a matter of routine experimentation. '623 patent at 14:31-33.

179. Because claim 1 of the '623 patent does not recite any activity, selecting the Miller '265 publication's Compound 102 based on its anti-cancer potency as raf kinase inhibitor conforms with at least one of sorafenib's inhibitory potencies.

180. Accordingly, it is my opinion that sorafenib as claimed in claim 1 of the '623 patent would have been obvious to a POSA and therefore claim 1 is invalid over a combination of Miller and what was known about 2-pyridinecarboxamide in further view of Armistead.

ix. Claims 2-6 Would Have Been Obvious to a POSA at the Time of Invention

181. Claim 2 of the '623 patent depends on claim 1 with the added limitation of the tosylate salt of sorafenib. Armistead teaches antiproliferative urea compounds and their pharmaceutically acceptable salts derived from pharmaceutically acceptable inorganic and organic acids also including tosylate. Armistead at 29:1-28. Pharmaceutically acceptable salts of Armistead's compounds include salts of inorganic or organic acids, e.g., inter alia, acetate, maleate, as well as tosylate and base salts, e.g., alkaline metal salts and the like. *Id.* It is my opinion that a POSA, seeking to provide pharmaceutically acceptable salts of organic acids of the sorafenib compound in view of (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with N-methylpicolinamide would produce the tosylate salt of Armistead as part of routine optimization based on a reasonable expectation of success, rendering claim 2 invalid under 35 U.S.C. § 103(a).

182. Claim 3 recites a pharmaceutical composition comprising sorafenib or a pharmaceutically acceptable salt thereof, and a physiologically acceptable carrier. As discussed above, Winkler or Armistead disclose a physiologically acceptable carrier such as sodium chloride

or sterile aqueous carrier among their pharmaceutically acceptable carriers. Accordingly, it is my opinion that claim 3 is invalid under 35 U.S.C. § 103(a) as rendered obvious in view of (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with N-methylpicolinamide or in further view of Armistead.

183. Claim 4 depends from claim 3 and further requires that the pharmaceutically acceptable salt is a tosylate salt. Accordingly, as discussed above in connection with claim 2, it is my opinion that claim 4 is obvious under 35 U.S.C. § 103(a) over (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with with N-methylpicolinamide or in further view of Armistead.

184. Claim 5 recites a tablet comprising sorafenib or a pharmaceutically acceptable salt thereof and at least one pharmaceutically acceptable excipient. As discussed above, Winkler, Haga, Armistead, the Miller '265 publication, the Miller '880 publication, all disclose utilizing their compounds in tablets, with pharmaceutically acceptable excipients including diluents. Accordingly, it is my opinion that claim 5 is invalid as obvious under 35 U.S.C. § 103(a) over (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with with N-methylpicolinamide.

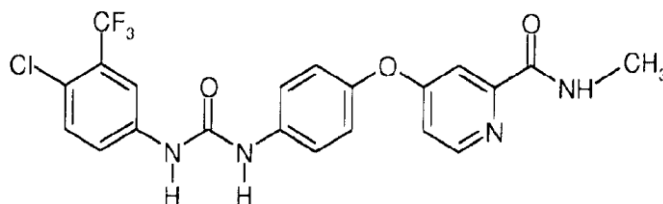
185. Claim 6 depends from claim 5 and further requires that the pharmaceutically acceptable salt is a tosylate salt. Accordingly, as discussed above in connection with claims 2 and 4, it is my opinion that claim 4 is invalid as obvious under 35 U.S.C. § 103(a) over (i) Winkler in view of Haga; (ii) Winkler in view of Armistead; (iii) Winkler in view of the Miller '265 publication; or (iv) Winkler in view of the Miller '880 patent, all in combination with with N-methylpicolinamide or

c. Invalidity of the '576 Patent

i. The Asserted Claims of the '576 Patent

186. It is my understanding that Plaintiffs have asserted claims 14-16 of the '576 patent against Defendants.

187. It is my understanding that, as set forth in the Certificate of Correction, claim 14 is an independent claim reciting the pharmaceutically acceptable salt of a compound selected from a group consisting of 2 compounds (claim 14), of which one compound in the list is sorafenib having the structure set forth below:



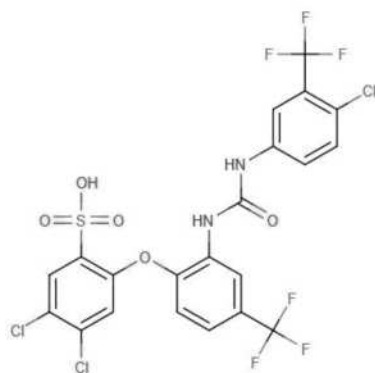
188. It is also my understanding that, as further set forth in the Certificate of Correction, claim 16 is also an independent claim reciting the pharmaceutically acceptable salt which is the tosylate salt of a compound selected from a group consisting of 2 compounds (claim 16), of which one compound in the list is sorafenib having the structure set forth above.

ii. Claims 14-16 of the '576 Patent Would Have Been Obvious to a POSA at the Time of the Invention

189. It is my opinion that claims 14-16 of the '576 patent are obvious in view of the prior art available at the time of the invention.

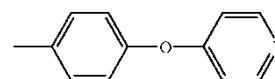
iii. Claim 14 of the '576 patent would have been obvious to a POSA in view of the Winkler, Miller PCT and Compound Optimization

190. As previously discussed, Winkler teaches urea compounds, which have antiproliferative properties against cancer cells. Winkler prefers Compound I^a, a urea compound having a trifluoromethyl moiety and a chloro moiety, which has improved antiproliferative properties against cancer. Compound I^a of Winkler is the urea compound shown below:



191. Sorafenib is a urea compound having a trifluoromethyl and a chloro moiety on one of its phenyl groups.

192. The urea compounds disclosed in the Miller PCT, just like those in the '576 patent, are inhibitors of the raf kinase pathway. The Miller PCT further discloses the p21^{ras} oncogene, a major contributor to the development and progression of human solid cancers, and that inhibition of raf kinase results in inhibition of active ras and thus, the inhibition of the growth of a variety of tumors. *Id.* at 2: 6-17. Like in the '576 patent (*id.* at 1:66-2:1), Miller PCT's aryl ureas include both aryl and heteroaryl analogues, which inhibit the raf pathway (*id.* at 2:19-20.). Both types of ureas have the same structural backbone.



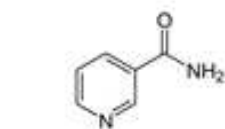
193. As discussed above, Miller PCT discloses Compound 102, which is a structure very similar to sorafenib but for an N-methylcarbamoyl moiety on the pyridine ring. Miller PCT lists 22 structures similar to Winkler's Compound I^a. However, based on R² of , tested in every compound permutation of Tables 1 and 2 of Miller PCT, it is my opinion that Compound 102 emerges as the natural lead compound.

194. It is my opinion that Miller PCT's Compound 102 has more than a mere structural similarity to sorafenib; it is recognized as a potent raf kinase inhibitor having an IC₅₀ of between 1 nM and 10 μ M. *Id.* at 74:20. It is my understanding that when the claimed invention and

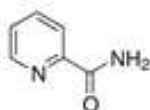
structurally similar prior art species share any useful property, that will generally be sufficient to motivate a POSA to make the claimed species.

195. Further, Miller PCT also discloses a combinatorial method for synthesis of diphenyl ureas using triphosgene which is similar to a method utilized in the '576 patent for the same purpose. Miller PCT at 59:4-17; '576 patent at 35:50, et seq. Accordingly, it is my opinion that Winkler in view of Miller PCT in combination with picolinamide or N-methylpicolinamide would render obvious sorafenib and thus invalidate all claims that recite it as a specie, namely claims 1, 5, 8, 11 and 14 of the '576 patent.

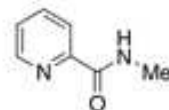
196. It was also known since at least September 5, 1989 that diphenyl ureas have poor solubility. (Haga at 26:3-4, Compound 53). It was also known since at least 1996, that nicotinamide and picolinamide have high solubility in water, 5×10^5 mg/L and 1.8×10^5 mg/L, respectively (data from SRC PhysProp Database).



Nicotinamide



Picolinamide

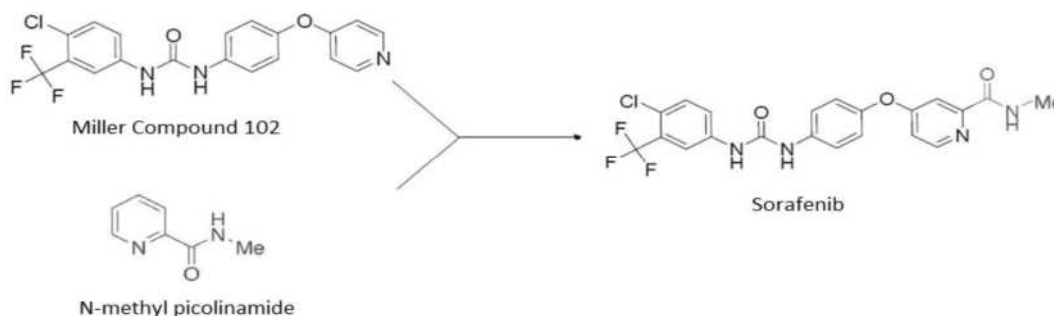


N-methyl picolinamide

197. It is my opinion that N-methylpicolinamide is an obvious derivative of picolinamide, which one of skill in the art seeking to enhance the solubility of a raf kinase inhibitor while maintaining its potency as a raf kinase inhibitor and improving binding in the enzyme receptor pocket would find it obvious to incorporate the N-methylcarboxamide structure into Miller PCT's Compound 102. *See* Lipinski.

198. Specifically, it is my opinion that to design a urea compound to treat cancer, one of ordinary skill in the art would find it obvious to make sorafenib by using Winkler's Compound I^a to select Miller PCT's Compound 102 and optimize it for increased solubility with the N-

methylcarbamoyl group knowing that N-methylpicolinamide enhances solubility of a compound, and one of ordinary skill in the art would arrive at sorafenib as illustrated below:



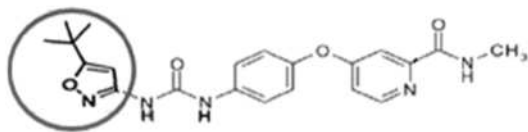
199. Accordingly, a POSA would have known that incorporating N-methylcarboxamide into Miller PCT's Compound 102 would enhance solubility of Compound 102 resulting in better bioavailability and also enhanced binding to the enzyme receptor pocket. Miller PCT also discloses pharmaceutically acceptable salts of his compounds, so that a pharmaceutically acceptable salt of sorafenib would have been obvious in the prior art.

200. For at least these reasons, it is my opinion that claim 14 of the '576 patent is invalid as obvious under 35 U.S.C. § 103(a) over the prior art of Winkler in view of Miller PCT and the and the compound optimization techniques that would encourage the incorporation of N-methylpicolinamide.

iv. Claim 14 of the '576 patent would have been obvious to a POSA in view of Miller PCT, Dumas PCT and Compound Optimization

201. In Compound 101, Dumas PCT describes an anti-cancer raf kinase inhibitor that has the same structure as sorafenib as claimed in the '576 patent, but for a 5-substituted-3-isoxazolyl group in lieu of a 4-chloro-3-(trifluoromethyl)phenyl substituent at the B position of the sorafenib A-D-B backbone. Dumas at 87.

202. As discussed above, the structure of Dumas PCT's Compound 101 is similar to sorafenib but for a 4-chloro-3-(trifluoromethyl)phenyl substituent at the B position of the A-D-B backbone, Dumas PCT has a 5-tert-butyl-3-isoxazolyl group shown above in a circle.



203. As in the Miller PCT and the '576 patent, Dumas PCT's compounds are asymmetrical substituted diaryl ureas that are useful to treat cancers by inhibiting raf kinase. In particular, as described in the '576 patent (*id.* at 1:66-2:1) and Miller PCT's aryl ureas, Dumas PCT's aryl ureas include both aryl and heteroaryl analogues, which inhibit the raf pathway (*id.* at 2:16-17) and are useful in treating solid cancers such as, for example, carcinomas (e.g., lungs, pancreas, thyroid, bladder or colon, myeloid disorders (e.g., myeloid leukemia) or adenomas (e.g., villous colon adenoma). *Id.* at 2:7-14.

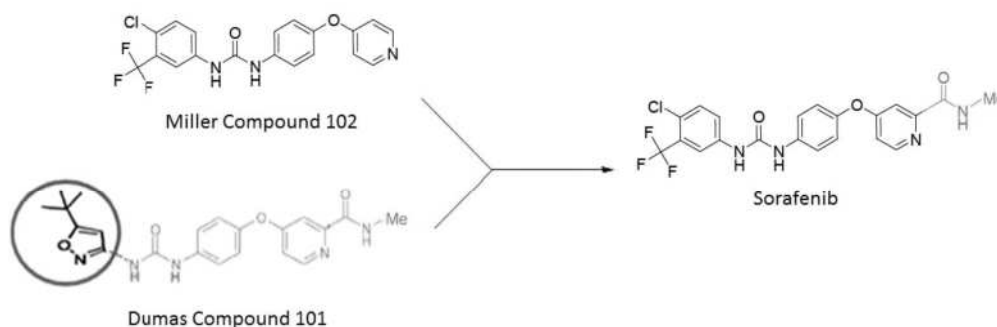


204. Additionally, both Dumas PCT's ureas and those recited in claim 14 of the '576 patent have the same structural backbone. Dumas PCT's ureas are illustrated as formula I: (*id.* at 2:21), wherein B is generally an unsubstituted or substituted, up to tricyclic, aryl or heteroaryl moiety with up to 30 carbon atoms with at least one 5 or 6 member aromatic structure containing 0-4 members of the group consisting of nitrogen, oxygen and sulfur. *Id.* at 2:22-25. Further, 2-(N-methylcarbamoyl)-4-chloropyridine disclosed by Dumas PCT (*id.* at 55:13-56:2), is the same compound as 4-chloro-N-methyl-2-pyridinecarboxamide used in the '576 patent in the synthesis of sorafenib or compound 42 disclosed in the '576 patent (*id.* at 46:16-20).

205. Both Miller PCT's Compound 102 and Dumas PCT's Compound 101 have very similar activity and are structurally similar, but also have many common co-inventors, and Dumas PCT teaches the efficacy of the N-methylcarbamoyl substituent² with respect to raf kinase

² Dumas PCT states that "[a]ll compounds exemplified displayed IC₅₀s of between 1 nM and 10 μM." *Id.* at 112:4.

inhibitory potency. Therefore it is my opinion that one of ordinary skill in the art would be motivated to modify Miller PCT's Compound 102 with Dumas PCT's Compound 101 to produce the claimed sorafenib compound as illustrated below:



206. It is also my opinion that the fact that both compounds, Miller PCT's Compound 102 and Dumas PCT's Compound 101, are potent raf kinase inhibitors, provides the motivation for modifying Miller PCT's Compound 102 with the N-methylcarbamoyl moiety present in Dumas PCT's Compound 101 to produce sorafenib as the skilled artisan would want to produce a potent raf kinase inhibitor. Accordingly, as discussed above, it is my opinion that Miller PCT in combination with picolinamide or N-methylpicolinamide or Miller PCT in combination with Dumas PCT would render obvious sorafenib and thus invalidate all claims that recite it as a specie.

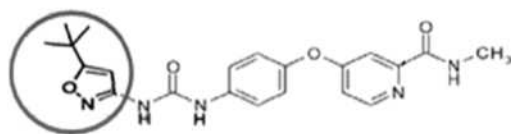
207. Further, Dumas PCT and Miller PCT also disclose pharmaceutically acceptable salts of their compounds, so that a pharmaceutically acceptable salt of sorafenib is obvious in the prior art.

208. For at least these reasons, it is my opinion that claim 14 of the '576 patent is invalid as obvious under 35 U.S.C. § 103(a) over the prior art of Miller PCT in view of Dumas PCT and the compound optimization techniques that would encourage the incorporation of N-methylpicolinamide.

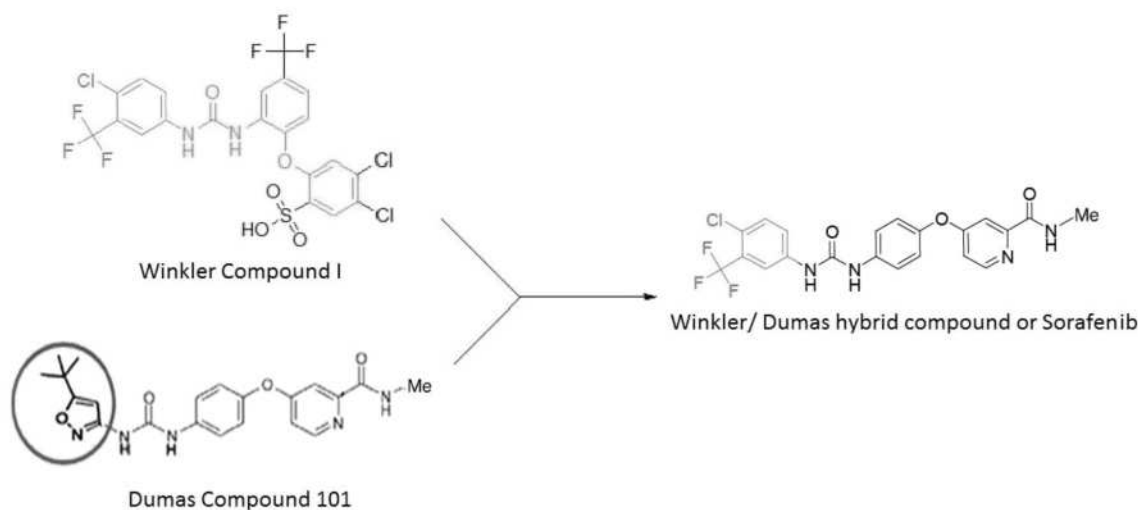
v. Claim 14 of the '576 patent would have been obvious to a POSA in view of Winkler, Dumas PCT and Compound Optimization

209. As discussed above, Dumas PCT teaches Compound 101 as the closest structure to Winkler's Compound I^a. Like Winkler's Compound I^a, Dumas PCT's Compound 101 has anti-cancer properties by inhibiting a raf kinase. Further, Dumas PCT's Compound 101 contains an N-methylcarbamoyl moiety, which one of ordinary skill in the art would recognize as a compound of enhanced solubility. It is my opinion that based on Winkler's Compound I^a, Dumas PCT's Compound 101 emerges as a natural lead compound for further investigation.

210. Specifically, by further applying Winkler's backbone structure of diphenyl or diaryl urea, it is my opinion that Compound 101 emerges as a preferred compound. In Compound 101, R² does not have any other substituents on its rings other than N-methylcarbamoyl which enhances its solubility. Dumas PCT at 80-93. As explained above, Dumas PCT's Compound 101 has the same backbone structure as sorafenib that is claimed in claim 14 of the '576 patent. By comparison to claim 14, Dumas PCT's Compound 101 is missing a 2-chloro-5-(trifluoromethyl)phenyl substituent at the B position of the A-D-B backbone where Dumas PCT has a 5-tert-butyl-3-isoxazolyl group shown below in a blue color circle:



211. Thus, it is my opinion that Dumas PCT's Compound 101 can be selected as a lead compound for further investigation based on its similarity to Winkler's Compound I^a and because it contains an N-methylcarbamoyl moiety which one of ordinary skill in the art would find useful to improve the solubility of a Winkler-Dumas PCT hybrid.



212. It is also my opinion that because Dumas PCT also discloses pharmaceutically acceptable salts of his compounds a pharmaceutically acceptable salt of sorafenib would have been obvious in the prior art.

213. For at least these reasons, it is my opinion that claim 14 of the '576 patent is invalid as obvious under 35 U.S.C. § 103(a) over the prior art of Winkler in view of Dumas PCT and the compound optimization techniques that would encourage the incorporation of N-methylpicolinamide.

vi. Claim 14 of the '576 patent would have been obvious to a POSA in view of Winkler, Haga and Compound Optimization

214. Claim 14 is obvious in view of Winkler, Haga, and compound optimization for the same reasons explained for the '834 and '623 patents.

vii. Claim 14 of the '576 patent would have been obvious to a POSA in view of Winkler, Armistead and Compound Optimization

215. Claim 14 is obvious in view of Winkler, Armistead, and compound optimization for the same reasons explained for the '834 and '623 patents.

viii. Claim 15 of the '576 patent would have been obvious to a POSA in light of the prior art.

216. Claim 15 is dependent directly or indirectly on, and incorporates, the limitations of claim 14, respectively, and cover sorafenib as a specie while specifying that the pharmaceutically acceptable salt can be a basic salt of an organic or inorganic acid or an acid salt of an organic or inorganic base. Based on my opinion with respect to claim 14, these claims are invalid under 35 U.S.C. § 103(a) as obvious over the prior art of (i) Miller PCT in combination with N-methylpicolinamide; (ii) Miller PCT and Dumas PCT in combination with N-methylpicolinamide; (iii) Winkler and Haga in combination with N-methylpicolinamide; or (iv) Winkler and Armistead in combination with N-methylpicolinamide for the same reasons as discussed above with respect to claim 14.

217. Moreover, as also discussed above, both Miller PCT, Dumas PCT and Armistead disclose pharmaceutically acceptable salts which can be either basic or acid salts as recited in claim 15. It is my understanding that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is obvious if one of them is taught in the prior art. Based on this understanding, it is my opinion that claim 15 is invalid under 35 U.S.C. § 103(a) as obvious over the prior art of (i) Miller PCT in combination with N-methylpicolinamide; (ii) Miller PCT and Dumas PCT in combination with N-methylpicolinamide; (iii) Winkler and Haga in combination with N-methylpicolinamide; or (iv) Winkler and Armistead in combination with N-methylpicolinamide for the same reasons as discussed above with respect to claim 14.

ix. Claim 16 of the '576 patent would have been obvious to a POSA in view of Miller PCT In Combination With Picolinamide or N-Methylpicolinamide or Miller PCT In Combination With Dumas PCT Further In View of Armistead

218. Claim 16 is a Markush style claim which recite, *inter alia*, the tosylate salt of sorafenib. Miller PCT, Dumas PCT and Haga broadly recite many pharmaceutically acceptable salts as discussed above, however, they do not specifically disclose a tosylate salt of their compounds. As discussed above, Armistead discloses compounds which have anti-cancer potency,

the same activity as that of sorafenib. In particular, Armistead teaches antiproliferative urea compounds and their pharmaceutically acceptable salts derived from pharmaceutically acceptable inorganic and organic acids also including tosylate. Armistead at 29:1-28. Pharmaceutically acceptable salts of Armistead's compounds include salts of inorganic or organic acids, e.g., *inter alia*, acetate, maleate, as well as tosylate and base salts, e.g., alkaline metal salts and the like. *Id.* at 29:1-28.

219. Accordingly, it is my opinion that a POSA, seeking to provide pharmaceutically acceptable salts of organic acids of the sorafenib compound as taught by (i) Winkler in view of Miller PCT; (ii) Winkler in view of Miller PCT and Dumas PCT; (iii) Winkler PCT in view of Dumas PCT; (iv) Winkler in view of Haga; or (v) Winkler in view of Armistead in combination with N-methylpicolinamide would produce the tosylate salt of Armistead as part of routine optimization based on a reasonable expectation of success. It is my opinion that making an active compound into a particular salt form such as tosylate is not inventive as it does not have any effect on its therapeutic efficacy.

220. Armistead also discloses tosylate as a known pharmaceutical salt of antiproliferative urea compounds. As such, it is my opinion that a POSA would find it obvious and have a reasonable expectation of success in producing the tosylate of sorafenib as taught by (i) Winkler in view of Miller; (ii) Winkler in view of Miller and Dumas PCT; (iii) Winkler in view of Dumas PCT; (iv) Winkler in view of Haga; or (v) Winkler in view of Armistead in combination with N-methylpicolinamide.

221. For at least these reasons, it is my opinion that claim 16 is invalid under 35 U.S.C. § 103(a) as obvious over the prior art as a POSA would expect to produce the tosylate salt of Armistead as part of routine optimization based on a reasonable expectation of success in light of (i) Winkler in view of Miller; (ii) Winkler in view of Miller and Dumas PCT; (iii) Winkler in view of Dumas PCT; (iv) Winkler in view of Haga; or (v) Winkler in view of Armistead, in combination with N-methylpicolinamide.

x. Claim 14 of the '576 Patent Would Have Been Obvious to Try a POSA at the Time of the Invention

222. It is my opinion that the modification of Winkler-Miller PCT, Winkler-Miller '880, or Winkler-Miller '265 publication, Winkler-Miller (PCT, '880 patent, or '265 publication)-Dumas PCT, Winkler-Dumas PCT, Winkler-Haga or Winkler-Armistead to make sorafenib further render claim 14 of the '576 patent obvious to try to a POSA.

223. As discussed above, both Miller PCT and Dumas PCT were familiar with combinatorial methods of synthesis of diphenyl ureas using triphosgene, which is similar to a method of preparing sorafenib disclosed in the '576 patent. Also as discussed above, both Miller PCT and Dumas PCT disclosed N-methylcarbamoyl substituted pyridines used in the preparation of sorafenib. Therefore, it is my opinion that the inventors of the '576 patent were familiar with combinatorial methods of synthesis for the development of a library of potential lead compounds whose structure-activity relationship (SAR) could be further explored vis-à-vis their raf kinase inhibitory potency and these compounds could be routinely optimized. Miller PCT at 59:4-17; Dumas PCT at 70:12-24. Further, since the Miller PCT inventors were familiar with the N-methylcarbamoyl substituted pyridine of Dumas PCT, and there were a finite number of compounds having raf kinase inhibitory potency (144 compounds disclosed in Miller PCT), it is my opinion that when working on the compounds of the '576 patent, the inventors would have found it obvious to test the inhibitory activity towards raf kinase of Miller PCT's Compound 102 having the N-methylcarbamoyl moiety on the pyridine ring found in Dumas PCT's Compound 101.

224. Additionally, as discussed above, it is my opinion that the desire to provide drug-like lead compounds having increased solubility while preserving raf kinase inhibitory potency and increasing its enzyme binding ability provides a motivation and reasonable expectation of success for adding an N-methylcarbamoyl moiety on the pyridine ring of Miller PCT's Compound 102 as taught for N-methylpicolinamide or Dumas PCT's Compound 101.

225. For at least these reasons, it is my opinion that claim 14 of the '576 patent are invalid as obvious to try.

xi. Admissions by Inventors in Later Publications and in the '576 Patent Further Support of Finding of Invalidity Under 35 U.S.C. § 103 as Obvious

226. It is my opinion that admissions by inventors in later publications further show that the development of sorafenib was the result of routine optimization and thus obvious. For example, in Khire's publication discussed above, which was authored by many of the inventors of the '576 patent, these inventors describe how their knowledge and use of combinatorial chemistry led to the routine "optimization" of the lead compound which led to a series of potent, orally active Raf-1 kinase inhibitors and that this culminated in the identification of a clinical candidate BAY 43-9006, which is sorafenib. Khire at 783-786.

227. Other co-inventors of the '576 patent, namely Lowinger, Dumas and Smith authored another publication with Wilhelm, also discussed above, in which they acknowledge that in 1994, when a team was assembled to develop sorafenib, the introduction and refinement of in vitro HTS and combinatorial chemistry greatly facilitated the development of new chemicals. Moreover, an assay for HTS identification of selective Raf/MEK/ERK enzyme inhibitors discovered by Glaxo-Wellcome was vital in identifying and selecting candidate raf kinase inhibitors for further evaluation for Phase I clinical trials. Wilhelm at 835-844. Against this background, it is my opinion that using HTS, ADME and known assay technologies to determine toxicology of various asymmetric ureas known as raf kinase inhibitors, the selection of Miller PCT's Compound 102 as a lead compound and modifying it with either a N-methylpicolinamide or Dumas PCT's Compound 101 would have been obvious to try, and mere routine optimization as acknowledged by the inventors in the Wilhelm and Khire publications.

228. Accordingly, it is my opinion that sorafenib as claimed in the '576 patent would have been obvious under 35 U.S.C. § 103 and therefore invalid over a combination of Miller's Compound 102 and 2-pyridinecarboxamide .

VIII. SUPPLEMENTAL OPINIONS

229. In the even that Plaintiffs should submit any response to my report, I reserve the right to respond to any issues raised by that response, including expert reports.

230. I specifically reserve my right to provide additional opinions regarding secondary considerations of nonobviousness. I understand that under the Scheduling Order in this case, Defendants need not address evidence of secondary considerations in their opening round of expert reports; rather, secondary considerations shall be addressed by Plaintiffs in the second round of expert reports, and Defendants shall respond to such evidence in the reply round of expert reports.

231. If called to testify, my testimony may include an explanation of scientific principles that underlie the opinions expressed in this report.

232. I have based my opinions and analyses on documents and information available to me at the time I signed the report. If and when any new evidence arises, I reserve the right to supplement or modify my opinions to reflect that evidence.

233. I reserve the right to prepare demonstratives to help explain my opinions.

A handwritten signature in black ink, appearing to read "Ron Bihovsky", is written over a horizontal line.

RON BIHOVSKY

APRIL 13, 2017